مركز التميز البحثي في التقنية الحيوية
Center of Excellence in Biotechnology Research

المؤتمر الدولي الرابع للمؤشرات الحيوية للأمراض المزمنة

THE 4th

INTERNATIONAL CONFERENCE OF BIOMARKERS IN CHRONIC DISEASES

FONDAZIONE GIOVANNI LORENZINI
GIOVANNI LORENZINI MEDICAL FOUNDATION
MILAN, ITALY HOUSTON, TX USA

BRP
برنامج أبحاث المؤشرات الحيوية
Biomarkers Research Program

Proceedings of the 4th ICBCD 2010

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MESSAGE FROM THE CHAIRMEN

Professor Omar Al-Attas

The recent exponential boom in the scientific research industry in the Kingdom of Saudi Arabia has boosted several opportunities to not only modernize the scientific and clinical communities in the region, but also to take lead as an emerging nation based on knowledge. The *Biomarker Research Program of King Saud University*, one of the pioneer scientific institutions for national health surveys, and a formidable leader in the development of clinical science research in the kingdom and the region, is both humbled and honored, to collaborate with *Giovanni Lorenzini Medical Science Foundation* (Milan, Italy and Houston, USA), a world-renowned foundation in the promotion of biomedical science, to co-organize the *4th International Conference on Biomarkers in Chronic Diseases*. This conference, being held for the first time in the Middle-East, is truly a unique platform where scientists and physicians' coming from the region can catch up and update themselves on what's latest in the fast emerging field of biomarkers in chronic diseases.

There is clear evidence that chronic non-communicable diseases are increasing in the developing world, including the gulf region. While the response of both the biomedical research and clinical communities elsewhere are equally aggressive in addressing the rising epidemics, ethnic diversity and environmental differences should be taken into account, and thus the need to customize management. This conference, through the generous approval of His Majesty, King Abdullah bin Abdulaziz Al-Saud and the Ministry of Higher Education, as well as the support of our respected speakers, is intended to equip us with the necessary knowledge on biomarkers that will eventually guide us in our future clinical decisions and scientific undertaking.

On behalf of the organizing committee, we encourage the participants to take advantage of this conference, in ways that will be of tremendous benefit to your future research and clinical management. We also welcome you to the bustling metropolis of royal Riyadh, the finest of the Arab cities.

PROFESSOR OMAR SALEM AL-ATTAS
Chairman
The 4th Intl. Conference on **BIOMARKERS in Chronic Diseases**
(Diabetes, Obesity and Cardiovascular Diseases)
4-6 May, 2010 (Riyadh, Saudi Arabia)

> *This conference, being held for the first time in the Middle-East, is truly a unique platform where scientists and physicians' coming from the region can catch up and update themselves on what's latest in the fast emerging field of biomarkers in chronic diseases*

MESSAGE FROM THE CHAIRMEN

Professor Rodolfo Paoletti

Clinical decision-making in the study of the individual patient or in risk stratification in populations, or in drug development in clinical trials demands increasingly more support from highly predictive diagnostic tools. The highly predictive value is even more critical in the clinical approach to chronic diseases, such as diabetes, obesity, atherosclerosis and their development to cardiovascular disease where scholars and clinicians are facing an increasing number of not always validate and context-specific qualified biochemical diseases markers and the pressure of innovation in biotechnology. Multimarker analysis and the integration of biochemical and bioimaging disease markers in cardiovascular diseases support clinical decision-making more than the use of biomarkers alone. There is an increasing need to understand, validate, and qualify the context specific use of the biochemical and bioimaging markers in the very demanding areas of diagnosis, prevention, and treatment of chronic diseases such as diabetes, obesity, and atherosclerosis.

> *There is an increasing need to understand, validate, and qualify the context specific use of the biochemical and bio-imaging markers in the very demanding areas of diagnosis, prevention, and treatment of chronic diseases such as diabetes, obesity, and atherosclerosis.*

Within the framework of the Project on Integrated Biochemical and Bioimaging Markers, the **Lorenzini Foundation**'s three previous meetings (Lugano 2005[1], Berlin 2007[2], and Seattle 2008[3]) have highlighted the critical issues related to the use of biomarkers to support the clinical decision making in the cardiovascular area. The three meetings have confirmed the need to analyze and to confront different clinical and research approaches and different best solutions in the use of biochemical and bioimaging markers. Further on, different geographic and ethnic specific patterns are asking for devoted approach to **local epidemiology realities** to better design protocols for diagnosis, prevention and treatment of cardiovascular patients. And thus the decision of *Biomarker Research Program of the College of Science, King Saud*

University in Riyadh (Saudi Arabia) and the *Giovanni Lorenzini Medical Science Foundation* (Milan, Italy and Houston, USA) to co-organize the Conference that is under the auspices of the prestigious King Saud University, internationally known as the Medical Master in science, medicine and health organization in favor not only of the Arab population.

This meeting is designed to provide a comprehensive and up-to-date overview of recent advances in the field of Integrated Biomarkers assessment and qualification in the context of diagnosis, treatment, and prevention of *Chronic Disease such as Diabetes, Obesity, Metabolic Syndrome, Cardiovascular Disease and Cardiometabolic Disorders.*

PROFESSOR RODOLFO PAOLETTI
Chairman
The 4th Intl. Conference on Biomarkers In Chronic Diseases
(Diabetes, Obesity and Cardiovascular Diseases)
4-6 May, 2010 (Riyadh, Saudi Arabia)

[1] *1st International Course Integrated Biomarkers on Biochemical And Bioimaging Endpoints In Cardiocerebrovascular Diagnosis, Prevention, Therapy, And Drug Development*, Lugano (Switzerland) - October 27-29, 2005
http://www.lorenzinifoundation.org/biomarkers2005/slides/

[2] II International Symposium on Integrated Biomarkers In Cardiovascular Diseases Berlin, Germany (June, 21-23, 2007) http://www.lorenzinifoundation.org/biomarkers2007/slides/

[3] 3rd International Symposium on Integrated Biomarkers In Cardiovascular Diseases (Seattle, WA, USA - July 9-11, 2008)
http://www.lorenzinifoundation.org/biomarkers2008/slides/

ICBCD 2010 Committees

OVER-ALL CHAIRPERSONS

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Dr. Nasser M. AL-Daghri (KSA)

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Professor Rodolfo Paoletti (ITALY)
Professor Andrea Peracino (ITALY)
Professor Sudhesh Kumar (UK)

General Information

…about Riyadh

Riyadh is the capital and largest city of Saudi Arabia. The city is located in the center of the Kingdom, and is affectionately called "*The Desert Pearl*"; although, it's actual name, "Riyadh" is derived from the Arabic word for "*garden*." As the capital city, Riyadh is home to all of the government ministries and foreign embassies. Riyadh is served by the King Khalid International Airport. It is approximately 1,061 km (660 miles) from Riyadh to Jeddah on the west coast, and approximately 447 km (278 miles) from Riyadh to Dhahran on the east coast.

Weather & Time

Located in the heart of the desert, Riyadh is hot and dry most of the year, though it can be quite cool over night in the winter. Riyadh is seven hours ahead of Eastern Daylight Time, and eight hours ahead of Eastern Standard Time.

Shopping

Riyadh is very modern, with many malls, office buildings, hotels, etc. Yet it hasn't forgotten its past - you can still visit older market areas ("souqs"), as well as the ruins of the old city of Diriyah, northwest of the city.

…about the venue

The 5-star Al Khozama Hotel is located in the upscale commercial and residential area of downtown Olaya. It's a complex that includes' apartments, office spaces, restaurants, leisure facilities and retail shopping. It offers 187 exclusive and stylish rooms, all comfortable and warmly decorated. The Al Khozama Hotel facilitates professional business and commercial exhibitions and meetings as par excellence and is famous for its outstanding hospitality services among other 5 Star Hotels in Riyadh, Kingdom of Saudi Arabia.
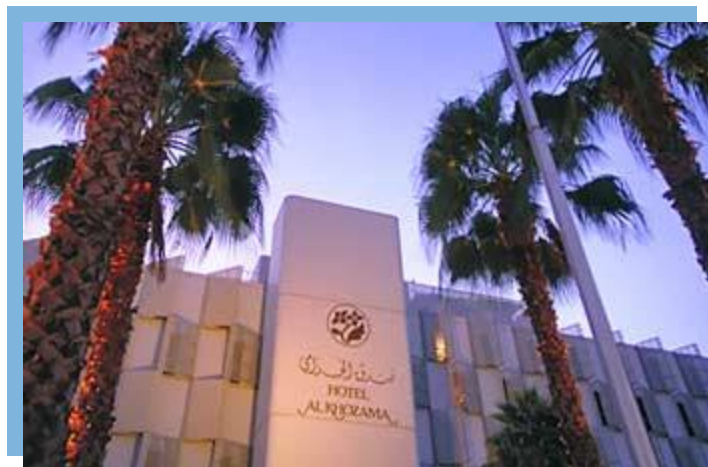
…about the university

The majestic and royal King Saud University (KSU) takes pride not only as the highest ranking university in the Middle East and the Arab World, but also as a leader in building a knowledge-based economy for the kingdom. Under the management of his Excellency, Prof. Abdullah Al-Othman, KSU has immediately risen to prominence as one of the fastest growing and most improved university in the world in the fields of science, humanities, arts and industries, without compromising its core foundation based on Islamic and cultural values. (www.ksu.edu.sa)

…about the Biomarker Research Program (BRP)

Formerly known as the Diabetes and Endocrinology Research Laboratory, BRP has been KSU's frontier in the advancement of biomedical science, and home to various kingdom-wide surveys and epidemiological studies. Founding director, Prof. Omar Al-Attas, and managing director, Dr. Nasser Al-Daghri, have successfully built a formidable research team guided by the world's topnotch researchers, making it an indispensable asset in the university's equally impressive academic stronghold. (http://biomark.ksu.edu.sa)

…about the Giovanni Lorenzini Medical Science Foundation

With more than 30 years of solid experience in of translational medicine, the Giovanni Lorenzini Medical Science Foundation based in Italy and USA, currently takes center stage as a renowned and well respected scientific foundation in the promotion of integrated biochemical and bio-imaging biomarkers that support clinical decision making in the prevention, diagnosis, and treatment of chronic non-communicable diseases. Under the leadership of Prof. Rodolfo Paoletti and Prof. Andrea Peracino, this foundation continues its noble goals in encouraging emerging scientists and clinicians to support a "holistic" approach in the management of diseases entities through the "customized" information provided by biomarkers.

Language

The official language of the conference is English.

Poster Exhibition

Posters will be displayed at the Exhibition Hall of the Al-Khozama Hotel on all days of the conference.

Sponsor Exhibition

The conference is accompanied by a major exhibition for the sponsoring companies according to the category-(ies).

Currency

Currency in Saudi Arabia is Saudi Riyals (SR). One US$ = 3.75 SR (approx). All major Credit cards are accepted in major establishments.

CME Accreditation & Certificates

Local CME credits will be given to participants. All participants will receive a certificate of participation on the last day of the conference. Certificates of Appreciation and other tokens of appreciation will be given to speakers.

DAY 1 TUESDAY (May 4, 2010)   AL-KHOZAMA MAIN AUDITORIUM

TIME	PROGRAM	
8:00-8:30	ON-SITE REGISTRATION	
SESSION I	CHAIR PERSONs **Omar Al-Attas (KSA) & John Albers (USA)**	
8:30-9:10	**TITLE**	**SPEAKER**
	INTEGRATED APPROACH TO BIOMARKERS PERSPECTIVE	**Andrea Peracino (ITALY)**
9:10-9:25	Serum Soluble BAG3 as a Biomarker for Heart Failure	**Margot de Marco (ITALY)**
9:25-9:40	Heat Shock Protein 70 and IgE are Early Predictors of Myocardial Ischemia and Recovery After Coronary Artery Disease Grafting (CABG)	**Amal Baalash (EGYPT)**
9:40-10:00	OPEN FORUM	
10:00-10:15	Coffee Break	
SESSION II	CHAIR PERSONs **Assim Alfadda (KSA) & Paul Thornalley (UK)**	
10:15-10:55	**THE ROLE OF BIOMARKERS IN CVD: WHERE DO WE STAND IN 2010?**	**Wolfgang Koenig (GERMANY)**
10:55-11:10	Urinary 8-Hydroxyguanosine as a Biomarker of Microangiopathic Complication in Type 2 Diabetic Patients	**Shereen Atef (EGYPT)**
11:10-11:25	Endothelial Nitric Oxide Synthase (eNOS) Gene Polymorphisms and their Application as Potential Genetic Biomarkers for Coronary Artery Disease in Saudi Population	**Khalid Alkharfy (KSA)**
11:25-11:45	OPEN FORUM	
11:45-12:15	OPENING CEREMONY AND EXHIBITION	
12:15-13:30	Lunch	
SESSION III	CHAIR PERSONs **Mansour Al-Nozha (KSA) & Yousef Al-Saleh (KSA)**	
13:30-14:10	**PHOSPHOLIPID TRANSFER PROTEIN AND SELECTED BIOMARKERS IN CARDIOVASCULAR AND ALZHEIMER'S DISEASE**	**John Albers (USA)**
14:10-14:25	Angiotensin Converting Enzyme (Ace) and Methylene Tetrahydrofolate Reductase (MTHFR) Gene Polymorphisms among Saudi Cases with Complicated Hypertension	**Ahmad Settin (EGYPT)**
14:25-14:40	Correlation of Peripheral Blood Flow, Plasma Vascular Endothelial Growth Factor, Fibroblast Growth Factor, Fatty Acid Synthase, Intercellular Adhesion Molecules, and Adrenomodullin in Diabetic Peripheral Vascular Disease	**Faten Zakareia (EGYPT)**
14:40-15:00	OPEN FORUM	

15:00-15:30	Coffee Break	
15:30- 17:00	MEET THE EXPERT CONSOLIDATED OR NOVEL BIOMARKERS: HOW TO CHOOSE? Andrea Peracino (Italy)	MEET THE LADY EXPERT DIABETES IN THE YOUNG PEOPLE AND ETHNICITY Santica Marcovina (USA)

DAY 2 WEDNESDAY (May 5, 2010)   AL-KHOZAMA MAIN AUDITORIUM

	TITLE	SPEAKER
8:00-9:00	POSTER PRESENTATION/EXHIBITION	
SESSION IV	CHAIR PERSONs **Nasser Al-Daghri (KSA) & Naila Rabbani (UK)**	
	TITLE	**SPEAKER**
9:00-9:40	**BIOMARKERS IN CLINICAL PRACTICE AND PHARMACODIAGNOSTICS**	**Rodolfo Paoletti (ITALY)**
9:40-9:55	The Arg-Gly Polymorphism in B2-adrenergic Receptor Gene is Linked to Obesity, Hypertriglyceridemia and Hyperleptinemia in Saudis	**Maha Daghestani (KSA)**
9:55-10:10	Elevated Erythrocyte Plasma Membrane Redox System is an Early Marker of Type 2 Diabetes Mellitus	**Syed Ibrahim Rizvi (INDIA)**
10:10-10:30	OPEN FORUM	
10:30-10:45	**Coffee Break**	
SESSION V	CHAIR PERSONs **Khalid Alharfy (KSA) & George Chrousos (GREECE)**	
10:45-11:25	**INTEGRATION OF MICROARRAY ANALYSIS INTO DRUG TARGET DISCOVERY**	**Lee Eiden (USA)**
11:25-11:40	Study of Protein Biomarker for DM Type 2 and Role of High Dose Thiamine on their Levels	**Samreen Riaz (PAKISTAN)**
11:40-11:55	Scal Atrial Natriuretic Peptide Gene Polymorphism and Hypertension in Tunisian Population	**Hayet Soualmia (TUNISIA)**
11:55-12:15	OPEN FORUM	
12:15-13:30	**Lunch** POSTER PRESENTATION/EXHIBITION	
SESSION VI	CHAIR PERSONs **Ali Al-Ghamdi (KSA) & Andrea Peracino (ITALY)**	
13:30-14:10	**BIOMARKERS OF CARDIOVASCULAR DISEASE AND INFLAMMATION IN YOUTH WITH TYPE 1 AND TYPE 2 DIABETES**	**Prof. Santica Marcovina (USA)**

TIME		
14:10-14:25	Adiposity and Insulin Resistance Correlate with Telomere Length in Middle-Aged Arabs: The Influence of Circulating Adiponectin	Shaun Sabico (KSA)
14:25-14:40	Application of Multiple Biomarkers to Risk Stratification in Type 2 Diabetes	Michael Kenna (USA)
14:40-15:00	OPEN FORUM	
15:00-15:30	Coffee Break	
15:30-17:00	MEET THE EXPERT INFLAMMATION, ATHEROSCLEROSIS AND OBESITY Filippo Crea (Italy)	MEET THE LADY EXPERT PROTEIN DAMAGE-BASED BIOMARKERS IN DIABETES Naila Rabbani (UK)
20:00	GALA DINNER	

DAY 3 THURSDAY (May 6, 2010)   AL-KHOZAMA MAIN AUDITORIUM

TIME	PROGRAM	
8:00-9:00	POSTER PRESENTATION/EXHIBITION	
SESSION VII	CHAIR PERSONs Majed Alokail (KSA) & Lee Eiden (USA)	
	TITLE	SPEAKER
9:00-9:40	ROLE OF INFLAMMATION BIOMARKERS IN PRIMARY PREVENTION	Filippo Crea (ITALY)
9:40:10:15	PROTEIN DAMAGE-BASED BIOMARKERS FOR METABOLIC CONTROL, RISK OF VASCULAR COMPLICATIONS AND THERAPEUTIC MONITORING IN DIABETES	Paul Thornalley (UK)
10:15-10:30	OPEN FORUM	
10:30-10:45	Coffee Break	
SESSION VIII	CHAIR PERSONs Mohammed Aldahmesh (KSA) & Santica Marcovina (USA)	
	TITLE	SPEAKER
10:45-11:25	BIOMARKERS FOR CHRONIC METABOLIC DISEASES	Sudhesh Kumar (UK)
11:25-12:00	BIOLOGICAL MARKERS OF SLEEP AND SLEEPING DISORDERS	George Chrousos (GREECE)
12:00-12:15	OPEN FORUM	
12:15-13:00	CLOSING CEREMONY	

INTEGRATED APPROACH TO BIOMARKERS PERSPECTIVE

ANDREA PERACINO[1]

[1]*Vice President - Fondazione Giovanni Lorenzini - Medical Science Foundation*

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Clinical decision-making in the study of the individual patient, in populations risk stratification, or in drug development, demands increasingly more support from highly predictive diagnostic tools. The highly predictive value is even more critical in the clinical approach to chronic disease, such as *diabetes, obesity, atherosclerosis* and their development to *cardiovascular disease* where scholars and clinicians are facing an increasing number of not always context-specific qualified biochemical diseases markers, and the pressure of bio-technology innovation. *Multimarkers* panels and the *integration of biochemical and bioimaging disease markers* in cardiovascular diseases support clinical decision-making more than the use of biomarkers alone. The burdens on life, disability and economy of *obesity, diabetes,* and *cardiovascular disease* in the countries justify the urgent need to improve the tools for their *diagnosis, treatment,* and *prevention.* In front of the clinical individualities of the mentioned pathologies, many pathophysiology areas, and consequent supporting tools to clinical decision making, are in common among *obesity, diabetes,* and *cardiovascular disease.   Glucose intolerance, insulin resistance, visceral adipose metabolism, adiponectin/leptin system, neuro-hormone, incretins, endothelial function, inflammation and acute reactant proteins, lipids disorders, atherosclerotic plaque development, thrombosis, myocardium conditioning*, must be deeply explored through appropriate tools as context qualified biomarkers. The biomarkers qualification requires context specific processes of technological assessment as*:* a) *Standardization of methods and technology;   b) Validation of their* *clinical usefulness; c) Validation of their cost/benefit ratios; d) Evidence – based support for their use in clinical trials; e) Criteria for qualification and transferability to the Standard Care.*

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SERUM SOLUBLE BAG3 AS A BIOMARKER FOR HEART FAILURE

MARGOT DE MARCO[1], Falco A[1], Festa M[1], Rosati A[1], Basile A[1], Turco MC[1]

Lab 1-56 Cellular Biochemistry, Department of Pharmaceutical Sciences, University of Salerno, Via Ponte Don Melillo, Fisciano, Italy

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The anti-apoptotic BAG3 protein is expressed at high levels in the cardiac tissue and, at lower levels, in other muscles. Our group has recently focused its interest on BAG3 protein produced in the myocardium. In the rats heart tissues was found a significant increase in BAG3 protein after induction of heart attack through a temporary coronary artery occlusion. Furthermore, we have evidences that BAG3 protein is released from cardiomyocytes when exposed to oxidative stress. Our results prompt us to examine whether BAG3 protein could be detectable in sera of patients affected by heart failure. To this end, we developed an ELISA test using BAG3 recombinant protein as calibrator. Sera were collected from blood donors and from 38 patients with clinical diagnosis of heart disease (of different types and severity) in order to analyze the soluble BAG3 protein concentrations in healthy subjects in respect to enrolled patients. In healthy individuals, detected BAG3 concentration mean value was 2.38 ng/ml ±0.32, while, the BAG3 concentration mean value in patients was 8.30 ng/ml ±0.58. The difference between patients with heart disease and healthy donors, is highly significant. Obtained data were also analyzed by a statistical program in order to define specificity and sensitivity values for this test. Taking as cut-off a value of 2.76 ng/ml, sensitivity and specificity were respectively 83.3% and 77.08%. In conclusion, our results indicate that BAG3 could be used as a biomarker for heart failure and considered for its diagnostic/prognostic potential in clinical practice.

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HEAT SHOCK PROTEIN 70 AND IGE ARE EARLY PREDICTORS OF MYOCARDIAL ISCHEMIA AND RECOVERY AFTER CORONARY ARTERY DISEASE GRAFTING (CABG)

AMAL A. BAALASH[1], Hamouda HE[1], Ibrahim BM[1], Yassein IK[1], Ismail GM[1]

King Saud Bin Abdul Aziz University, Riyadh, Saudi Arabia

Correspondence: abaalash@kfmc.med.sa

Introduction & Hypothesis: Cardiac markers of "minor myocardial damages" in patients with stable angina pectoris (SAP) are not confirmed; also the recovery markers after CABG surgery are also not well established. We assessed the hypothesis that heat shock protein 70, total Ig E, and MMP-9 which are proteins sharing in the inflammatory response after myocardial tissue damage and in tissue recovery, could be used as possible indicators for minor myocardial damages, and we also studied their usefulness in assessment of the success of CABG surgery in improving the myocardial ischemia. *Method:* Heat shock protein 70, IgE, MMP-9 , creatine phosphokinase-MB (CPK-MB), and lactate dehydrogenase (LDH) levels were measured in normal subjects (n=20), and in patients with chronic stable angina pectoris who were referred for elective CABG, before and after performing CABG-surgery (n=20). *Results:* Compared with normal subjects, increased heat shock protein 70 and IgE levels but not MMP-9, CPK-MB, and LDH were found in the pre-operative patient group. Heat shock protein 70, and IgE levels in the post-operative period were significantly reduced when compared to the pre-operative period. *Conclusion:* Heat shock protein 70 and IgE could be used for detection of early minor myocardial damage, as significant changes in their levels appear before any changes in the levels of MMP-9, CPK-MB and LDH. Besides, heat shock protein 70, and IgE returning to the normal levels after CABG surgery, suggests that they could be helpful to evaluate the effect of CABG surgery.

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THE ROLE OF BIOMARKERS IN CVD: WHERE DO WE STAND IN 2010?

WOLFGANG KOENIG[1]

[1] *Department of Internal Medicine II – Cardiology, University of Ulm Medical Center, Ulm, Germany*

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Current prediction of coronary heart disease (CHD) has certain limitations which relate mainly to the reduced number of risk factors evaluated by the various scores and in particular the imperfect prediction based on LDL blood levels which still presents a main criteria for intervention and target for therapy. Additional factors based on the INTERHEART study may complement our view of potentially modifiable risk factors but still leave an incomplete situation. This has formed the basis for a continued interest in a number of blood biomarkers, markers of subclinical disease, and genetic markers to further improve risk stratification for cardiovascular outcomes. However, today there is still an ongoing controversy regarding the clinical utility of these various biomarkers and last year a position paper has been published in Circulation putting together the necessary criteria for a standard reporting of biomarker studies and also describing the necessary statistical performance measures for risk estimation besides determination of relative risk. Such measures include e.g. discrimination based on c-statistics, calibration looking into the closeness of predicted probability to observed, and finally, and possibly most importantly for the clinical situation, reclassification of events based on additional testing. The presentation will illustrate these continuing problems in the application of such criteria in several studies using blood biomarkers, markers of subclinical disease, and genetic markers. It will discuss where we stand today and what is still needed in the future for better assessment of the clinical utility of emerging biomarkers as additional tools in risk stratification, monitoring of disease progression, but also in the selection of potential treatment targets, and response to therapy.

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URINARY 8-HYDROXYGUANOSINE AS A BIOMARKER OF MICROANGIOPATHIC COMPLICATION IN TYPE 2 DIABETIC PATIENTS

SHEREEN HASSAN ATEF[1]

Department of Clinical Pathology and Internal Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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Objective: This study aims to evaluate urinary 8-OHdG as a marker for diabetic micro angiopathic complications and to correlate its levels with the severity of diabetic nephropathyand retinopathy. **Methods:** The study included 50 patients with type 2 diabetes mellitus and 30 non-diabetic age and sex-matched controls. Urinary 8-OHdG, urine creatinine and urinary albumin excretion rate (UAE) rate were measured in all patients and control subjects. Both 8-OHdG and UAE rate were assayed by immunoassays. Assessment of glycemic control in patients was achieved by measurement of HbA1c. All of the patients underwent direct ophthalmoscopy and photography with pupils dilated. **Results:** There was a highly significant difference between different groups of type 2 diabetic patients classified according to retinopathy, and controls as regard 8-OHdG ($p < 0.01$), and albumin/creatinine (alb/creat) ratio ($F = 5.2$, $p < 0.01$). Patients classified according to alb/creat ratio revealed a highly significant difference regarding 8-OHdG, ($F = 5.2$, $p < 0.01$). Also, there was a significant difference between patients with microalbuminuria as regard 8-OHdG excretion [71.3 ± 11.8 versus 53.0 ± 18.5, respectively ($p < 0.05$)]. Similarly, a significant difference between patients with microalbuminuria regarding 8-OHdG excretion [71.3 ± 11.8 versus 26.1 ± 8.1 respectively ($p < 0.01$). There was also a significant difference regarding 8-OHdG between patients without retinopathy and those with simple retinopathy, and a highly significant difference between the same marker between patients without retinopathy and those with proliferative retinopathy. Using ROC curve, the diagnostic utility of 8-OHdG in discrimination of diabetic patients with retinopathy from those without at a cut-off of 34.4 µg/gm creatinine and a diagnostic sensitivity of 92.9 % and specificity of 86.4 % and efficacy of 90.0%. **Conclusion:** Measuring 8-OhdG is a novel convenient method for evaluating oxidative DNA damage. Diabtic patients, specifically those with advancing neuropathy and retinopathy had significantly higher that such changes may contribute to the development of microvascular complications of diabetes.

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ENDOTHELIAL NITRIC OXIDE SYNTHASE (ENOS) GENE POLYMORPHISMS AND THEIR APPLICATION AS POTENTIAL GENETIC BIOMARKERS FOR CORONARY ARTERY DISEASE IN SAUDI POPULATION

KHALID M. ALKHARFY[1], Al-Daghri N[2], Al-Attas O[2], Alokail M[2], Draz H[2], Hussain T[2]

[1]*Clinical Pharmacy Department, College of Pharmacy,* [2]*Biomarker Research Program, Biochemistry Department,*

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Endothelial nitric oxide synthase gene polymorphisms, either independently or through gene environmental interactions, are associated with cardiovascular diseases in multiple ethnic populations. However, no information is available with regard to such associations in Saudi population despite a high incidence of cardiovascular abnormalities. Here we aimed to study the associations of 894G> T and -786T> C polymorphisms of endothelial nitric oxide synthase gene with coronary artery disease in Saudi population. Variants 894G> T and -786T> C were studied in 142 coronary artery disease patients and 145 normal controls by PCR- restriction fragment length polymorphism analysis and allele specific PCR respectively. Carriers of GT and TT genotypes of 894G> T polymorphism were significantly high (p< 0.0001) in patients (47.2%, and 7%, respectively), than in controls (27.6% and 4.8%, respectively). Likewise, carriers for TC and CC genotypes of -786T> C polymorphism were significantly high (p< 0.001) in patients (50% and 32%, respectively) than in controls (34.5% and 22.5%, respectively). Both 894G> T [OR (95% CI); 4.39 (1.69-11.42)] and -786T> C [OR (95% CI); 2.74 (1.02-7.32)] variants were independently associated with the disease status. Genotype distributions of 894G> T and -786T> C polymorphisms in the disease and control populations matched with those found in Caucasian populations. This study, for the first time, suggests an independent association of 894G> T and -786T> C polymorphisms of endothelial nitric oxide synthase gene with coronary artery disease in Saudi population.

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PHOSPHOLIPID TRANSFER PROTEIN AND SELECTED BIOMARKERS IN CARDIOVASCULAR AND ALZHEIMER'S DISEASE

JOHN J. ALBERS[1]

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We address the questions whether LDL cholesterol is the best initial biomarker to target for treatment or therapy for patients at high risk for coronary artery disease (CAD) and is low HDL cholesterol the best biomarker to target to reduce the residual risk remaining after LDL reduction therapy? Proteomic analysis of HDL reveals at least 48 HDL-associated proteins. One of the HDL proteins is phospholipid transfer protein (PLTP), an important modulator of lipoprotein metabolism. PLTP has been shown to be increased in CAD, obesity and type 2 diabetes. Studies in mice have suggested that PLTP is atherogenic, and efforts to develop drugs to inhibit PLTP are under consideration. However, increased plasma PLTP activity may not be a mediator of CAD. Therefore, targeting a biomarker associated with CAD may not necessarily be beneficial, as we observed that PLTP reduces pro-inflammatory cytokines in human macrophages. Also, plasma PLTP complexes contain numerous proteins linked to immunity and inflammation. Currently, a combination of cerebrospinal fluid (CSF) biomarkers, such as increased phosphorylated tau and decreased Aβ42, magnetic resonance imaging, and positron-emission tomography, show promise in the early detection and diagnosis of Alzheimer's disease (AD). We have found that low CSF PLTP activity is associated with AD and inflammatory neurological diseases. Furthermore, PLTP reduces the level of phosphorylated tau in neuronal cells. These findings suggest that inclusion of other markers, such as PLTP, may increase our ability to detect pathological processes associated with neurodegeneration, as well as provide an opportunity to monitor treatment responses.

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ANGIOTENSIN CONVERTING ENZYME (ACE) AND METHYLENE-TETRAHYDROFOLATE REDUCTASE (MTHFR) GENE POLYMORPHISMS AMONG SAUDI CASES WITH COMPLICATED HYPERTENSION

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This work was planned to test for the association of polymorphisms related to methyltetrahydrofolate reductase (MTHFR) and angiotensin converting enzyme (ACE) genes with complicated hypertension in Saudi cases from Qassim region. Subjects included 117 cases (78 males and 39 females) who were hospitalized for hypertensive complications. Of these cases, 65.2% had cardiac affection, 17.9% had renal dysfunction while 83.8% were obese, 12.6% were smokers, 46.4% had diabetes, 22.5% had a positive family history of hypertension, 32.4% had positive parental consanguinity. For comparison, 169 normal healthy unrelated subjects (78 males and 91 females) from the same locality were taken as controls. For them DNA was extracted followed by real-time PCR amplifications for identification of MTHFR C677T, A1298C and ACE I/D gene polymorphisms. Cases showed significantly higher ACE mutant D allele carriage rate than controls (98.2 vs. 94.1% respectively, p<0.001). Cases showed a higher carriage rate for MTHFR 677 mutant T allele 1298 mutant C allele but both were statistically nonsignificant. Cases subgroups showed nonsignificant difference regarding the frequency of studied genotypes and alleles. The combined haplotype ACED/ 677C/1298A was significantly lower among cases than controls (p<0.001) that can be considered a protective haplotype whereas ACEI/ 677C/ 1298A and ACEI/ 677C/ 1298C haplotypes were found significantly higher in cases that can be considered susceptibility haplotypes. It is concluded that affected Saudi subjects with hypertension have certain genetic markers as the ACE I allele, MTHFR T and C alleles that can cause a high predisposition to the development of complications.

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CORRELATION OF PERIPHERAL BLOOD FLOW, PLASMA VASCULAR ENDOTHELIAL GROWTH FACTOR, FIBROBLAST GROWTH FACTOR, FATTY ACID SYNTHASE, INTERCELLULAR ADHESION MOLECULES, AND ADRENOMODULLIN IN DIABETIC PERIPHERAL VASCULAR DISEASE

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Background: We investigated Ankle/brachial index (A/BI), plasma vascular endothelial growth factor(VEGF), human basic- fibroblast growth factor (b-FGF), soluble fatty acid synthase (s-Fas), intercellular adhesion molecules (ICAM), adrenomedullin(ADM) and ghrelin in diabetic peripheral vascular disease(PVD). **Methods**: Thirty control and 60 type 2 diabetic women (mean age 45 ± 3.9 years, duration of diabetes 10.1 ± 2.1 years) were investigated. Diabetics without complications (group II),and with vasculopathy (group III) were diagnosed depending on clinical findings and abnormal Ankle/brachial index (A/BI).Plasma levels of VEGF, b-FGF, s-Fas, ICAM, ADM and ghrelin were measured. **Results**: A/BI showed significant decrease in diabetic PVD, while significant increase of plasmaVEGF, s-Fas, ICAM and ADM were observed in diabetic PVD (p= <0.05), b-FGF and ghrelin levels were comparable in all study groups (p = >0.05) A positive correlation was found between A/BI and VEGF and ADM , and a negative correlation with s-Fas and ICAM .Linear regression analysis revealed that VEGF, s-FAS (as independent variable) were not predictors for A/BI in vasculopathy. While the analysis revealed ICAM as a predictor for A/BI. **Conclusion:** The positive correlation of VEGF with A/BI elucidates its vascular protective and direct impact role on blood flow in diabetic PVD. VEGF may be a good candidate for clinical use in PVD. Our study supports the notion of the protective role of ADM in PVD, although, its precise role is still to be elucidated. ICAM as a predictor and an early marker for diagnosis of diabetic PVD, supports the role of inflammation in pathogenesis of diabetic vasculopathy. b-FGF and ghrelin have no causative or compensatory role in PVD. So diabetic PVD is the result of multiple factors, it is optimistic to believe that reversing s-Fas or ICAM will halt vasculopathy, targeting multiple mechanisms simultaneously by administering combination treatments of VEGF, antiapoptotic drugs with or without ADM may be prospective .

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BIOMARKERS IN CLINICAL PRACTICE AND PHARMACODIAGNOSTICS

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Atherosclerosis process starts intra-arterially and becomes intraluminal. Imaging is the ideal method of diagnosis and monitoring. Therefore surrogate markers, such as *Carotid Intima Media Thickness*, have shown to be reliable. In an attempt to improve better evaluation of atherosclerosis process, considerable effort has been made in the discovery and characterization of soluble biomarkers which can go beyond the measure of total- and LDL-cholesterol levels. Biochemical markers (among them *C-reactive protein* (CRP), for instance) not only provide new important diagnostic and prognostic information, but may be useful to determine the pathological role of *inflammatory circulating molecules* in the development of atherosclerotic lesions. Moreover, biological markers may serve to identify new patients at risk of cardiovascular disease, to monitor the efficacy of antiatherosclerotic treatments, and to develop new pharmacological tools for the treatment of atherosclerosis. In randomized clinical trials *Biomarkers Stratified Designs* maximize the advantage of randomization by providing unbiased estimates of benefit to risk ratios for the entire randomly assigned population. Nevertheless, a pharmacological treatment capable of decreasing their plasma levels, as related to a reduction of cardiovascular events, may also help to establish their value in atherogenesis. Multiple screening of different biomarkers may therefore improve the assessment of risk, diagnosis, and prognosis for cardiovascular disease. In addition, soluble biomarkers have been shown to be modulated by hypolipidemic drugs and to be potentially useful in determining the clinical benefits of pharmacological therapies that do not alter serum lipid levels.

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THE ARG-GLY POLYMORPHISM IN B2-ADRENERGIC RECEPTOR GENE IS LINKED TO OBESITY, HYPERTRIGLYCERIDEMIA AND HYPERLEPTINEMIA IN SAUDIS

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The β2-adrenergic receptor (ADRB2) is a major lipolytic receptor in human fat cells, and several studies in different populations, have shown association between codon 16 polymorphism of the ADRB2 gene and obesity. In this study we conducted a case-control investigation to determine association between ADRB2 gene polymorphisms at codons 16 and obesity in Saudi individuals. The study included 329 non-related individuals [males: 109 (33.1%) and females: 220 (66.9%)], age ranging from 18 to 36 years. Anthropometric measurements were carried out and body mass index (BMI) was calculated. Metabolic parameters (glucose, triglyceride, cholesterol, HDL- and LDL-cholesterol, insulin and leptin) were determined using commercially available kits or autoanalysers. The Arg16Gly polymorphism was investigated in each individual by polymerase chain reaction (PCR) amplification of the DNA segment containing codon 16 of the ADRB2 gene, followed by DNA sequencing. The subjects were divided into three groups (normal weight, overweight and obese) according to BMI and the levels of the metabolic parameters and frequency of Arg16Gly polymorphism were obtained separately for each group. Overweight and obese subjects had a significantly higher frequency of Gly16 compared with normal weight subjects and there were no differences in the frequency in males and females. The subjects carrying Gly16 allele regardless of BMI had greater total fat mass, waist and hip circumference, W/H ratio, cholesterol, triglyceride, low-density lipoprotein cholesterol and plasma leptin, compared with those without the Gly16 allele. Our findings provide strong evidence that Arg16Gly polymorphism is associated with obesity in the Saudis and influences lipid phenotypes and leptin levels in overweight/obese subjects.

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ELEVATED ERYTHROCYTE PLASMA MEMBRANE REDOX SYSTEM IS AN EARLY MARKER OF TYPE 2 DIABETES

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Introduction: Diabetes mellitus is strongly associated with oxidative stress. Human erythrocytes contain a plasma membrane redox system (PMRS) which transfers electrons from intracellular donors to extracellular acceptors. The PMRS which incorporates an ascorbate free radical (AFR) reductase provide a redox system that enables the cells to effectively counteract oxidative processes. **Hypothesis**: Oxidative stress precedes the development of disease in first degree relatives of type 2 diabetic patients. **Methods**: The study involved measurement of erythrocyte membrane PMRS and AFR reductase activity in normotensive subjects (n = 22) of age ranging between 30-45 with ≥ one parent diagnosed with type 2 diabetes (Rel T2D). The activity of PMRS and AFR reductase was compared with age and sex matched controls (n = 25) and type 2 diabetic patients (T2DM) (n = 21). **Results**: We present evidence that erythrocyte PMRS activity is increased in Rel T2D (14.76 %) and in type 2 diabetic patients (37.53 %). The increase in the activity of erythrocyte AFR reductase was 23.16 % in Rel T2D and 38.34 % in T2DM. **Conclusion**: These findings show that an impaired redox balance may be a cause for disturbance of homeostasis in type 2 diabetic families even before the development of the disease. The increase of erythrocyte PMRS and AFR reductase signifies compensatory mechanisms to mitigate increased oxidative stress. Elevated erythrocyte PMRS and AFR reductase may be used as markers to predict the development of disease.

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MICROARRAY-BASED GENE DISCOVERY AND ITS APPLICATION TO CHRONIC DISEASE

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Identifying targets for therapeutics, and biomarkers for monitoring and detecting disease, can involve similar routes to discovery. Transcriptomic analysis of gene expression differences in normal and disease states using DNA microarray is a case in point. This lecture focuses on gene expression changes that occur during progression from one cell state to another, emphasizing the transitional transcriptome and identification of individual gene products meriting further investigation as therapeutic targets, biomarkers, or both. Identifying cell culture systems that can be induced to undergo a transition associated with disease (neurodegeneration, transformation, insulin resistance, etc) is advantageous, because transitional transcripts may be co-expressed clinically with end-state gene expression unlinked to disease progression per se, even when stages of disease progression can be distinguished. Signaling pathways for enhancement, or repression, of gene transcription identified in cell culture models provide potential targets based on pharmacological abrogation of expression of specific target genes. Linking gene expression to cellular outputs can identify genes whose silencing confirms functional significance, a first step in target validation for therapeutics development versus biomarker development. In vivo microarray analysis in both intact and gene-deficient animal models for disease is a logical next step, to assess tissue targeting with respect to treatment pharmacodynamics and biomarker sampling. Translation to clinical practice, as well as reverse translation from clinical observation to engineering disease in animal models, can be aided by bioinformatic approaches that create a pipeline for systematic identification of likely biomarkers for disease progression as well as individual candidates for drug intervention.

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STUDY OF PROTEIN BIOMARKER FOR DIABETES MELLITUS TYPE 2 AND ROLE OF HIGH DOSE THIAMINE ON THEIR LEVELS

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Background: This research work describes the levels of protein biomarkers specific to diabetes mellitus type 2 and effect of high dose thiamine on these levels. **Methods:** Type 2 diabetic patients, age and sex-matched normal healthy controls were recruited from Sheikh Zayed Hospital, Lahore, Pakistan. Plasma proteins were analysed by 2-D liquid chromatographic system in which samples were initially fractionated by chromatofocusing and the selected fractions were further analysed by reverse-phase chromatography. The proteins which showed variation between test and control samples were identified by MALDI TOF analysis. Analysis of all the samples belonging to the control, placebo and thiamine treated groups were then analyzed for the four proteins which were found to vary, by ELISA. **Results:** Levels of apolipoprotein A-I was found to decrease by -6.4 % while apolipoproetin-E, leptin and C reactive protein (CRP) were found to increase by +802, +218 and +872 %, respectively in the diabetic patients as compared to the controls. The level of CRP decreased by 63% after thiamine therapy as compared to the controls and the placebo while other protein markers did not show a significant change after the therapy. **Conclusion:** Since CRP level variation has been reported in other pathological sates, role of thiamine may have a significant bearing on the prognosis of such diseases.

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SCAI ATRIAL NATRIURETIC PEPTIDE GENE POLYMORPHISM AND HYPERTENSION IN TUNISIAN POPULATION

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Background: Atrial natriuretic peptide (ANP) is involved in blood pressure regulation by its vasodilator and natriuretic effects. Abnormalities in the ANP system could play a key role in the genesis of hypertension. Several variants of ANP gene have been identified in humans. The ScaI is a restriction site loss in the ANP precursor gene as the substitution of a T for C at position 2238 led to translation of ANP with two additional arginines. In this study, we evaluated the impact of the ScaI ANP gene polymorphism on hypertension in a sample of the Tunisian population. **Methods**: We genotyped 365 patients with hypertension and 392 healthy controls. The ScaI ANP gene polymorphism was determined by polymerase chain reaction-restriction fragment length polymorphism analysis. Alleles were separated on agarose gels stained with ethidium. **Results**: We observed no significant differences in genotype distribution and allele frequency between patients and controls in the total population and by sex. The frequencies of A2 wild T and C A1 mutant allele were 0.48 and 0.52 in the hypertensive group and 0.49 and 0.51 in normotensive subjects (p=0.66). The odds ratio (95% CI) of hypertension was not significant 0.63 [0.38-1.05] (p=0.07) for TC heterozygotes and 0.76 [0.39-1.44] (p=0.40) for CC homozygote. Correction for age, gender, body mass index, fasting glucose, creatinine, uric acid, dyslipidemia strengthened the estimate. The clinical characteristics were not related to the T2238C polymorphism in multivariate analysis. **Conclusion**: From the present study, we conclude that the ScaI ANP gene polymorphism is not a marker for hypertension in the Tunisian population.

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BIOMARKERS OF CARDIOVASCULAR DISEASE AND INFLAMMATION IN YOUTH WITH TYPE 1 AND TYPE 2 DIABETES

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Until the early 1990s, diabetes in youth was almost exclusively type 1 diabetes (T1D). Type 2 diabetes (T2D) was almost exclusively diagnosed in older individuals and rarely observed in pediatric centers. However, concomitantly with the rising prevalence of obesity in youth, T2D is commonly diagnosed in the pediatric population. Early onset T2D (age of diagnosis 18-44 years) has been associated with more aggressive cardiovascular disease (CVD) than later onset T2D suggesting that CVD complications in youth with T2D may be even more unfavorable. We have evaluated lipid and lipoprotein levels, preponderance of small, dense LDL, apoB levels and other novel CVD risk factors such as IL-6, hsCRP, fibrinogen, adipocytokines and microalbuminuria in a young cohort (age 10-22 years) with T1D or T2D and in a control group of non-diabetic youth. Youth with T1D and optimal glucose control had lipid levels comparable to those in the control group, while higher apoB levels and more small, dense LDL were observed regardless of glycemic control. Compared with controls, T1D youth had higher IL-6 and fibrinogen levels independent of glucose control while hsCRP levels were significantly higher only in T1D youth with poor glycemic control. Compared with controls, youth with T2D had a higher prevalence of all major CVD risk factors. Adjustment for body mass index and glucose control substantially lowered the differences in CVD risk factors between cases and controls except for fibrinogen and IL-6 which remained significantly higher. These results indicate that adiposity and glycemia are important contributors to the observed differences in CVD risk profile among T2D and control youth while inflammatory and prothrombotic factors appear to play an independent role.

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ADIPOSITY AND INSULIN RESISTANCE CORRELATE WITH TELOMERE LENGTH IN MIDDLE-AGED ARABS: THE INFLUENCE OF CIRCULATING ADIPONECTIN

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Background/objective: Studies in obesity have highlighted adipocytokines in the development of insulin resistance, which in turn may lead to accelerated aging. In this study, we determined associations of chromosomal telomere length (TL) to markers of obesity and insulin resistance in middle-aged adult male and female Arabs with and without diabetes mellitus type 2 (DMT2). **Design and Methods**: 193 non-diabetic and DMT2 subjects without complications (97 males and 96 females) participated in this cross-sectional study. Clinical data, as well as fasting blood samples, were collected. Serum glucose and lipid profile were determined using routine laboratory methods. Serum insulin, leptin, adiponectin, resistin, TNF-alpha and PAI-1 were quantified using customized multiplex assay kits. hsC-reactive protein and Angiotensin II (ANG II) were measured using enzyme-linked immunosorbent assays. Circulating leukocyte TL was examined by quantitative real time PCR. **Results**: Circulating chromosomal leukocyte TL had significant inverse associations with BMI, systolic blood pressure, fasting insulin, HOMA-IR, LDL- and total cholesterol, ANG II and hsCRP levels. Adiponectin, BMI, systolic blood pressure and LDL-cholesterol predicted 47 % of the variance in TL (p < 0.0001). HOMA-IR was the most significant predictor for TL in males, explaining 35 % of the variance (p = 0.01). In females, adiponectin, accounted for 28 % of the variance in TL (p = 0.01). **Conclusion**: Obesity and insulin resistance collectively influence chromosomal telomere length among adult Arabs with and without DMT2. The positive association of adiponectin to TL has clinical implications as to the possible protective effects of this hormone from accelerated aging.

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APPLICATION OF MULTIPLE BIOMARKERS TO RISK STRATIFICATION IN TYPE 2 DIABETES

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Introduction: Improved identification of subjects at high risk for development of Type 2 diabetes (T2D) could focus preventive interventions on those individuals who would benefit most. This presentation will summarize the performance of a multimarker Type 2 diabetes mellitus risk stratification test, the Diabetes Risk Score (DRS), and summarize the pros and cons of biomarker-based risk stratification compared to traditional methods. **Hypothesis:** Biomarkers have the potential to capture the complexity of chronic disease at an individual level, and to outperform population-based risk factors. **Methods:** The DRS is based on a 7-biomarker panel developed from the Inter99 cohort, a Danish longitudinal population-based study of middle-aged participants. The panel was tested on an independent population, the Botnia cohort, a Finnish family-based study designed to identify genetic factors associated with the development of T2D. Performance was evaluated by discrimination, calibration and reclassification against all risk factors available in the study, including OGTT, FPG, triglycerides, family history, waist, BMI and epidemiological risk scores. **Results:** In no case did classical risk scores outperform the DRS. Detailed comparisons demonstrate marginal performance improvements might be gained by using postprandial tests (OGTT). **Conclusion:** A panel of biomarkers improves the ability to identify individuals at risk of developing T2D. This study demonstrates that biomarker panels are practical clinical alternatives to traditional risk scores.

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ROLE OF INFLAMMATION BIOMARKERS IN PRIMARY PREVENTION

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Biomarkers of inflammation have a number of applications in the cardiovascular field. For this purpose, C-reactive protein holds much promise. C-reactive protein reports on inflammation regardless of the instigator. This very 'non-specificity' may underlie much of C-reactive protein's utility in risk prediction; C-reactive protein integrates overall inflammatory status, capturing aspects otherwise difficult to measure directly. For example, assessment of 'lifestyle' variables presents a practical challenge in the clinic. C-reactive protein may provide an overall readout that incorporates such otherwise difficult to quantitate elements associated with risk. Indeed, C-reactive protein may reflect low-grade chronic infections in various sites such as bronchitis and periodontitis or genetically determined hyper-reactivity of inflammatory cells, which can exacerbate atherosclerosis. Furthermore, recent studies have implicated risk factors not included in the Framingham Heart risk score, like abdominal obesity, psychosocial factors, sedentary lifestyle, low fruit and vegetable intake, and lack of alcohol consumption in a large proportion of population attributable risk for myocardial infarction. C-reactive protein levels associate with all these risk factors not accounted for by most current risk algorithms. Capturing these elusive risk components might contribute to the ability of high-sensitivity C-reactive protein to re-stratify many individuals deemed at intermediate risk of cardiovascular events by traditional risk calculators, into higher, or equally importantly, lower risk categories. This adjustment has major implications for preventive practice. Indeed, while high-risk subjects merit pharmacological treatment, the effectiveness of drug therapy remains uncertain in the intermediate risk category.

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PROTEIN DAMAGE-BASED BIOMARKERS FOR METABOLIC CONTROL, RISK OF VASCULAR COMPLICATIONS AND THERAPEUTIC MONITORING IN DIABETES

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Damage to the proteome by glycation, oxidation and nitration is a continual process in human tissues and body fluids. Glycation by both glucose and reactive dicarbonyl metabolites such as methylglyoxal increases in diabetes. Oxidative and nitration damage also increases as a consequence of oxidative stress in diabetes. Damaged proteins undergo cellular proteolysis excreting signatures of protein damage as glycated, oxidised and nitrated amino acids in plasma and urine. Studies to date have shown these signatures to be biomarkers related to metabolic control, risk prediction of vascular complications and quality of therapeutic intervention. Methylglyoxal forms glycation adducts mainly in arginine residues – hydroimidazolone MG-H1. Urine excretion of MG-H1 is responsive to both fasting and postprandial hyperglycaemia and is potentially a more responsive marker to changes in glycaemic control than glycated haemoglobin HbA1c. Urinary fluxes of glycated, oxidised and nitrated amino acids are potentially useful biomarkers of risk of vascular complications. Urinary excretion of MG-H1 correlated with protein damage in renal glomerular, peripheral nerve and retina in experimental diabetes. In the Joslin kidney study of type 1 diabetic patients with >10 years follow-up, urinary excretion of selected glycated and oxidised amino acids were risk predictors of early decline in renal function. These and similar measurements guided dosage of angiotensin II receptor blocker therapy to decrease protein damage and metformin to decrease risk of atherosclerosis. Increased validation and use of protein damage biomarkers for assessment of metabolic control, risk of vascular complications and therapeutic monitoring in clinical diabetes is expected in the future.

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BIOMARKERS FOR CHRONIC METABOLIC DISEASES

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There are now a plethora of guidelines for management of diabetes, obesity and cardiovascular diseases. Despite this the management of these conditions remain suboptimal. Our current model that relies on big "block-busters" drugs used according to common protocols for all patients may have reached the limit of effectiveness. This is particularly true of management of hyperglycaemia in type 2 diabetes and for obesity management. Further improvements in the management of these conditions will require earlier diagnosis, better risk profiling and the development of personalised medicine. The principal requirement for successful practice of personalised medicine is excellent high quality diagnostics, to enable the correct diagnosis of disease sub-types to be made. The role of biomarkers that may be genetic, biochemical or serological will be discussed. Novel approaches to development of biomarkers, including the use of imaging and the use of gases as biomarkers will also be discussed. Personalised medicine may still be a dream for metabolic diseases, but the intermediate step of "stratified" medicine may be possible in the near future.

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BIOLOGICAL MARKERS OF SLEEP DISORDERS, METABOLIC, INFLAMMATORY AND STRESS STATES: WHAT ARE THE COMMON DENOMINATORS?

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Sleep is essential for life in mammals and, us humans, spend approximately one third of our lives sleeping. Sleep and wakefulness are linked to the circadian clock and its *zeitgebers* and function diurnally in succession and mutual opposition of each other. Like other vital systems of the organism, the systems that subserve sleep and wakefulness are both located in the central nervous system (CNS), particularly the hypothalamus and the brainstem. Wakefulness is attained by the Arousal System, ie the Locus Ceruleus (LC) and the reticular formation, which together with the autonomic system and the hypothalamic-pituitary-adrenal (HPA) axis, are also components of the Stress System, that is activated when any stressor exceeds a certain threshold. The need of the organism for sleep is expressed as somnolence (sleepiness, sleep propensity), while the need for tissue rest and recovery from exertion is expressed as fatigue. Somnolence and fatigue are frequently confused with each other, however, they are different feelings subserved by different neural pathways and substrates. Cytokines and adipokines, such as TNF-a and Interleukin(IL)-6, are both somnogenic and fatigogenic, while Stress System mediators, including the key neurotransmitter of the LC and sympathetic system norepinephrine, as well as corticotropin-releasing hormone (CRH) and cortisol, are stimulating wakefulness and arousal. Thus, states associated with hypercytokinemia, such as infections, inflammatory disorders and central obesity, are frequently associated with excessive daytime sleepiness (EDS) and fatigue, while states associated with Stress System activation, such as situational apprehension, anxiety disorders and melancholic depression, are frequently associated with sleep disturbances, including insomnia, early morning awakening, frequent awakenings, etc. We have shown that lack of sleep in normal individuals is associated with elevated circulating somnogenic cytokines, such as IL-6, while stress is associated with elevated CRH, catecholamines and cortisol, all of which promote wakefulness and disturb sleep. We have also shown that patients with central obesity and insulin resistance, or even lean patients with polycystic ovaries and insulin resistance, suffer from sleep apnea, have increased circulating cytokines/adipokines, and suffer from EDS and fatigue. Thus, sleep apnea and EDS and fatigue appear to be components of the Dysmetabolic Syndrome. In contrast, we have shown that patients with idiopathic insomnia have Stress System hyperactivity with elevated CRH, catecholamine and cortisol production throughout the 24h, with the highest difference from normal controls in the evening hours. Interestingly, in the same patients, the plasma levels of inflammatory cytokines are also elevated, especially in the evening. In these patients we have the seemingly paradoxical combination of insomnia with fatigue, apparently because both arousal and somnogenic/fatigogenic mediators are elevated. We conclude that sleep disorders share biological markers with metabolic, inflammatory and stress sates.

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IMPROVED HIDDEN MARKOV MODEL IN DNA SEQUENCE ALIGNMENT

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We present an improved hidden-M arkov-Model (HMM) based method for performing global alignment of non-coding DNA sequences. The method uses an explicit model of length frequency distribution which can be specified, and allows any time reversible model of nucleotide substitution. The method uses a deterministic global optimiser to find the alignment with the highest posterior probability. We test in simulations, and compare it to a previous Monte Carlo based method, that performed very well in a previous simulation study. We show that the pair HMM methods have excellent performance for all combinations of parameter values we have considered an accurate explicit model than heuristic methods, but is computationally slower. The advent of automated DNA sequencing methods has resulted in an enormous growth in the volume of sequence data deposited in public databases. The increasing availability of genome sequence data for many related organisms offers great opportunities to study gene function and genome evolution, but it also presents new challenges for DNA sequence analysis, especially for non-coding DNA sequences .A useful alignment method must produce biologically meaningful and accurate alignments, and also must do so quickly. There is a trade-off because the most biologically realistic scoring functions are difficult to optimize.

EFFECT OF USING ESSENTIAL OILS AS A NATURAL ANTIOXIDANT WITH HEATED COTTONSEED OIL ON LIPID PROFILES

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Oils are subjected to many changes during food processing resulting to changed characteristics that produce harmful effects on lipids profiles of humans, thus increasing risk of cardiovascular diseases and cancers. To reduce and protect oils from such, synthetic antioxidants are added, but research have proven the side effects of these synthetic chemicals. It is important to replace these artificial antioxidants with natural ones to protect human health. The biological evaluation of cottonseed oil with the added essential oils (thyme, cinnamon and peppermint oils) in rat diet 42 days to indicate its effect on rats' serum lipids profiles was carried out. Determination was measured by GC-Mass spectrometry. Results revealed that the superiority of essential oils over the control, heated and TBHQ reduce total lipids, total cholesterol, and atherogenic factor. On the other hand it was obvious that the addition of TBHQ or using the heated oil only without any additions had inferior effects on blood lipid picture compared to the natural essential oils. It was found that thymol and p-Cymene are the major constituents of thyme oil 52% and 31%, respectively. Also, cinnamaldehyde 72% is the principal compound in cinnamon oil, while menthol 65%was the major component of peppermint oil. It could be concluded that adding essential oils improve the blood lipid profiles in most cases so it can be used as natural antioxidants .There is a need for further research on the effects of adding essential oils as natural antioxidants in humans.

BIOCHEMICAL SIGNIFICANCE OF SMALL DENSE LDL MEASUREMENT IN ASSESSING THE RISK FOR CAD USING SIMPLE PRECIPITATION METHOD

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Recently, small dense LDL has been highlighted as an important risk factor for coronary artery disease (CAD). The predominance of small dense LDL particles has been frequently correlated with increased triglycerides (TGs), and low HDL-cholesterol (HDL-C). Indeed, it is known that the TG concentration is inversely associated with LDL size. Methods for measurement of sd LDL are too laborious for clinical use. In our work we used a new technique that quickly quantifies sd LDL concentration, the precipitation method. This method will be discussed. The accuracy of our method was compared with the measurement of LDL size using a conventional method Polyacrylamide Gradient Gel Electrophoresis (PAGGE). Using the precipitation method we found a significant positive correlation between sd LDL concentration and TG levels ($r = 0.323$, $p<0.000$), which was coherent with our findings using PAGGE where the TG levels negatively correlated with size of LDL in our subjects ($r = -0.424$, $p=<0.000$). Furthermore, a significant negative correlation was found between LDL size and concentration of sd LDL determined using the precipitation method ($r = -0.207$, $p<0.021$). These results suggest that measurement of small dense LDL by precipitation method is useful to evaluate atherogenic risk and may be applicable to routine clinical examination in the Omani population. Finally, the few limitations of the precipitation method will be discussed.

BIOMARKERS OF OBESITY IN PREPUBERTAL CHILDREN AS POSITIVE PREDICTIVE VALUES IN DIAGNOSTICS AND THERAPY

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Inflammation and increased oxidative stress are potential mechanisms proposed to play a major role in morbidity-associated with obesity. This study aims to investigate the relationship between serum concentrations of the C-Reactive Protein (CRP), lipids, lipoproteins and obesity and visceral adiposity in children in pre-pubertal period. Baseline measures for age, BMI, lipid-lipoproteins levels and CRP in children was determined, considering gender, ethnicity, and family history of early obesity. Overweight was defined as at or above the 95th percentile of sex-specific body mass index (BMI). Obesity is associated with oxidative stress and can be reduced with weight loss, caloric restriction or antioxidant rich diets. Authors confirmed the association between obesity, ethnicity, and laboratory lipids, lipoproteins and CRP outcomes. Children with obesity have higher CRP and fats levels in prepubertal stage in age of ten to twelve years. There were not differences between girls and boys. The positive associations of obesity and visceral adiposity with elevated lipids , lipoproteins and CRP levels suggest the importance of reducing obesity and visceral adiposity to prevent elevations in lipids levels. Oxidative stress may be the unifying mechanism underlying the development of comorbidities in obesity in children. Metabolomics, Lipidomics, and Glycomics are also the most commonly used as techniques in identification of biomarker in obesity.

RENAL RESISTIVE INDEX AND URINARY N-ACETYL-B-GLUCOSAMINIDASE AS PREDICTORS OF EARLY RENAL INVOLVEMENT IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Urinary N-acetyl-b-glucosaminidase (NAG) is an indicator of the functional status of the renal tubules. The resistive index (RI) is thought to correlate with the severity of renal damage and to predict the rate of progression to end-stage renal disease. The aim of this study was to investigate whether changes in renal function assessed by urinary NAG and proteinuria are present in hypertensive patients and the association of these changes with RI assessed by ultrasound Doppler. 78 patients (36 males and 42 females) with essential hypertension of≥5years duration and normal serum creatinine were included compared with 57 subjects as controls. Total proteins, NAG and creatinine in urine were measured .RI was evaluated by ultrasound Doppler of the inter-lobar arteries. Hypertensive patients have significantly higher BMI, serum uric acid, NAG, proteinuria and RI. RI is shown to be significantly correlated with age, systolic blood pressure, hypertension duration, NAG, proteinuria, total cholesterol and creatinine clearance. In multivariate analysis RI was significantly and independently influenced by age, SBP, NAG and creatinine clearance. In conclusion, urinary NAG and proteinurea are elevated in hypertensive patients with normal serum creatinine and creatinine clearance. RI index is associated with these abnormalities, its change could be regarded as a marker of early renal damage and helps to identify hypertensive patients for whom more aggressive preventive and therapeutic measure are advisable.

ELEVATED SERUM POLYMORPHONUCLEAR ELASTASE IN OBESE PREHYPERTENSIVE WOMEN: IMPACT ON RESPIRATORY FUNCTION

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The study aims to correlate serum levels of elastase in obese pre-hypertensive women with pulmonary function tests. Thirty obese pre-hypertensive and 30 obese normotensive women, matched for age with 30 healthy controls. Body mass index (BMI), waist circumference (WC), blood pressure, lipid profile, high sensitivity C- reactive protein (hs-CRP), serum polymorphonuclear elastase (PMNE), and pulmonary function tests including forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio were assessed. Serum PMNE levels were significantly higher in pre-hypertensive and normotensive obese women than in controls. FEV1, FVC and FEV1/FVC ratio in both pre-hypertensive and normotensive obese women were significantly reduced compared to controls. In obese pre-hypertensive women, there were significant positive correlations between PMNE and BMI, WC, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein cholesterol, hs-CRP and negatively correlated with high density lipoprotein cholesterol, FEV1, FVC and FEV1/FVC. Serum PMNE concentration is elevated in obese pre-hypertensive women and its levels are correlated with inflammatory markers, dyslipidemia and air flow dysfunction. It can be used as an early marker for the development of pre-hypertension and predict occurrence of lung function impairment in obese subjects.

GENETICS OF CHILDHOOD OBESITY

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Obesity is determined by genetic, environmental and behavioral factors acting through the physiological mediators of energy intake and energy expenditure. Body weight is the archetypical trait, a quantitative phenotype that usually fails to display a Mendelian pattern of inheritance because it is influenced by many different loci. The concept that environmental factors operate on an underlying pool of genes that contribute to obesity susceptibility has important implications for our approach to the prevention and treatment of obesity. In severely obese children and adults, investigations should be directed at identifying endocrine, neurological and genetic conditions, followed by therapy and genetic counseling if appropriate. This study included 30 obese children and adolescents, 21 of which were males (70%) and 9 were females (30%). Their BMIs were above 95th percentile for age with mean BMI of 35 and mean BMI standard deviation of +7.26. Among the 30 studied cases, 17 had syndromic obesity (56.67%), 7 had simple obesity (23.33%) and 6 had monogenic obesity (20%). The 17 cases with sydromic obesity consisted of 8 cases with Bardet Biedl syndrome, 8 with Prader-Willi syndrome and 1 with Alström syndrome. Six cases had monogenic obesity, 4 of which had congenital leptin deficiency while the other 2 had congenital leptin receptor deficiency.

STUDY THE RELATIONSHIP BETWEEN INTERCELLULAR ADHESION MOLECULES (ICAM) AND INSULIN RESISTANCE AMONG TYPE II EGYPTIAN DIABETIC PATIENTS WITH NEPHROPATHY

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Type II diabetic patients usually present with endothelial dysfunction. Reduction of endothelial function in type 2 diabetic patients stimulates inflammation and increases the levels of circulating soluble adhesion molecules (Intercellular adhesion molecules (ICAM)). Cell adhesion molecules are important in promoting the inflammatory response. The aim of the present study is to determine plasma concentrations of ICAM-1 as a marker for endothelial activation among type 2 diabetic patients with or without nephropathy and also to explore the relationship between plasma levels of ICAM-1 and insulin resistance. This study included 70 subjects; 50 patients with T2DM were divided into two groups; those without complications (N = 20), and those with nephropathy (N = 30), and a control non-diabetic group (N = 20) without a family history of DM. Mean sICAM-1 level was significantly higher in the diabetic patients with nephropathy than in those without nephropathy and controls. A positive correlation between ICAM-1 & insulin resistance was observed. It can be concluded that the association between ICAM-1 expression and insulin resistance is consistent with clinical evidence relating insulin resistance, inflammation & levels of sICAM-1, suggesting that sICAM-1 may play a role in the development of diabetic nephropathy and can be used as a marker for early diagnosis of nephropathy as a major diabetic complications.

EVALUATION OF PLASMA ENDOTHELIN-1 AND SERUM INFLAMMATORY MARKERS IN PATIENTS WITH DIABETIC RETINOPATHY

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This study aimed to examine the role of ET-1 in the progression of diabetic retinopathy and to detect the relationship between stages of diabetic retinopathy and inflammatory activity. 55 type 2 diabetic patients were included. They were divided into 3 groups: Group I included 15 patients who had no retinopathy, Group II had 20 patients with non-proliferative diabetic retinopathy of varying severity and Group III had 20 patients with proliferative diabetic retinopathy. Another 20 healthy, age and sex-matched subjects served as controls. Plasma levels of glucose & ET-1, serum levels of IL-6, CRP, haptoglobin, α-1 antitrypsin, ALT, and AST were determined. Results showed that plasma level of ET-1 was increased significantly in group II & group III as compared to control, the highest level detected in group III. There was a significant positive correlation between ET-1 and both of the IL-6 and CRP ($p<0.05$) ($r = 0.389$ and 0.623 respectively). Best cut off values of ET-1 in group I was 1.32 pg/ml (sensitivity 80% & specificity of 90%). In group II it was 1.51 pg/ml (sensitivity 95% & specificity of 100%). In group III, it was 1.63 pg/ml (sensitivity 100% and specificity of 100%). Positive and negative predictive values in the studied groups were (90.9% and 82.6%, 100% and 95.24%, and 100% and 100% respectively). In conclusion, ET-1 plays a role in the development of diabetic retinopathy together with markers of inflammation. It may be helpful to predict presence of proliferative diabetic retinopathy. Identification of markers for vascular disease in diabetes is significant in the prevention of long-term disabilities and containing health care costs.

THE CORRELATION BETWEEN SOME TRACE ELEMENTS AND ATHEROSCLEROSIS IN MALE ALBINO RATS

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This study was designed to investigate the role of zinc and copper as non-traditional risk factors for CVD and to determine the effect of their supplementation either alone or together in rats with experimental atherosclerosis. It has been ascertained that in animals fed atherogenic diets, there was a statistically significant increase in serum total lipids, cholesterol, triacylglycerols, low density lipoproteins cholesterol (LDL-Ch), very low density lipoproteins cholesterol (VLDL-Ch) and a markedly significant decrease in high density lipoproteins cholesterol (HDL-Ch). A significant augmentation of serum copper values accompanied by a marked lowering of serum zinc level was detected. Heart copper and various organ's zinc concentrations were significantly reduced as compared with control group. Dietary supplementation of copper and zinc formula was the best over other tested formulae concerning reducing different lipid markers except HDL-Ch which was increased, reducing the atherogenic index and modulating zinc level in serum and organs. On the other hand, copper and zinc deficient diets were worst as it significantly increased atherogenic lipids, markedly decreased the anti atherogenic lipid and extremely elevated the atherogenic index. Overall, trace elements perturbations such as zinc and copper predispose to atherosclerosis. Dietary supplementation by both zinc and copper in adequate level plays a crucial role in reducing the extent of atherosclerosis.

VON WILLEBRAND FACTOR (VWF) PLASMA LEVEL AND MICROALBUMINURIA PREDICTOR FOR DIABETIC NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

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This study aimed to assess effects of vWf levels and microalbuminuria on the progression of diabetic nephropathy. Levels of fasting blood glucose, HbA1c, serum triglyceride, serum cholesterol, serum HDL-cholesterol, serum creatinine and GFR were evaluated. The study included 130 subjects. Group I (N =34) served as control group (mean age 27.2 ± 7.4 years). Group II (N = 96) were patients with type 2 diabetes mellitus (mean age 52.7 ± 6.7 years). Group II was further subdivided according to the presence of microalbuminuria. There was a significant increase in age, weight, blood glucose, lipid profile, vWF, urinary albumin, total protein, HbA1C, serum creatinine, blood urea, and GFR in patients with T2DM (group II) versus group I. In group II, microalbuminuria was found in 92.7%, high vWF in 17.7%, and low GFR in 51% of patients. In group II, vWF was strongly correlated with GFR and microalbuminuria. There was a significant difference in age, duration of T2DM, HbA1C, serum creatinine and GFR in patients with high vWF than those with normal vWF. Patients with abnormal GFR had a highly significant difference in age, duration of diabetes, weight, vWF, urinary albumin, HbA1C, serum creatinine and GFR compared to those with normal GFR. In patients with low GFR, there was a high prevalence of increased vWF and microalbuminuria. In T2DM patients with microalbuminuria, 45% patients were in stage I, 39.7% in stage II and 15.7% were in stage III of renal affection. In conclusion, the risk of renal damage among microalbuminuric T2DM patients is much higher when a high vWF concentration is present. Microalbuminuria in T2DM can occur in the absence or the presence of a generalized endothelial dysfunction, and that the latter is a much more malignant' condition than the former.

DETECTION OF ADVANCED GLYCATION ENDPRODUCT IN IMMUNOGLOBULIN G OF PATIENTS WITH DIABETIC COMPLICATIONS USING ANTISERUM AGAINST GLYCATED POLY-L-LYSINE

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Aim: Oxidative cleavage of Amadori-lysine products is a major route to N^ϵ-carboxymethyllysine (CML), an advanced glycation endproduct (AGE). In the present study, reactive oxygen species (ROS) modified Amadori-rich glycated poly-L-lysine was used to probe AGE adducts in Immunoglobulin G (IgG) in type 2 diabetes patients with secondary complications. **Methods:** UV, CD, IR and NMR spectroscopy were applied to characterize hydroxyl radical modified glycated poly-L-lysine, previously determined by ROS inhibitors. Sera of 11 patients with chronic hyperglycemia and long-term history of type 2 diabetic complications (diabetic nephropathy, retinopathy and atherosclerosis) and of other 11 patients with the same clinical profile but without any secondary complications have been analyzed. 10 healthy subjects were taken as control. IgG was purified from sera of the subjects by affinity chromatography. Antiserum against the modified poly-L-lysine was developed in experimental animals and induced antibodies were characterized by solid phase immunoassay. **Results:** CML formation in ROS modified glycated poly-L-lysine was confirmed by the spectral techniques of IR and NMR. Anti-ROS-glycated poly-L-lysine antiserum showed appreciable recognition of the diabetic IgG as well as the *in vitro* ROS modified glycated IgG while there was no significant recognition of IgG from the normal subjects. **Conclusions:** ROS induced structural perturbations in glycated lysine residues of IgG may be involved in eliciting immune response against diabetes IgG, leading to autoantibody production in the diseased patients. In conclusion, IgG containing AGE-adducts could serve as a potential biomarker for type 2 diabetes and as a risk factor for the disease complications.

BAG3 IS RELEASED INTO THE EXTRACELLULAR ENVIRONMENT AFTER STRESS AND ACTIVATES MACROPHAGES

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A family of co-chaperone proteins that share the BAG domain are able to interact with Hsp70 and are involved in a number of cellular processes, including proliferation and apoptosis. Among these, BAG3 is receiving increased attention due to its high levels in several disease models and its inducible expression during cell response to stressful conditions (i.e. high temperature, heavy metals, and certain drugs). BAG3 has been recently found in soluble forms or in membrane-associated forms, furthermore its presence is detectable in sera of human subjects affected by heart failure. In the present study, we examined whether extracellular BAG3 plays a role in various physiological and pathophysiological conditions such as immunoregulatory and inflammatory processes. To analyze the possible activity on the immune response, we administered recombinant BAG3 to J774 (murine macrophage cell) coltures; the activation of macrophages was evaluated by expression of inducibile isoform of nitrite oxide syntase (INOS) and nitrite production. Recombinant BAG3 increased nitrite production in respect to untreated cells (p $\geq$ 4.14 E-05) in a dose-dependent manner. The BAG3 protein interaction with J774 cell surface was demonstrated by conjugating recombinant BAG3 with a fluorophore and subsequent observation by confocal microscope. In conclusion, obtained data suggest a possible role of extracellular BAG3 in regulating the immune response.

ACTIVITIES OF GPX AND CAT BEFORE AND DURING DEVELOPMENT OF HYPERTENSION IN YOUNG SHR

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Glutathione peroxidase (GPx) and catalase (CAT), the two main enzymes involved in the detoxification of hydrogen peroxide (H_2O_2), have been implicated in the pathogenesis of hypertension. We hypothesized that this endogenous H_2O_2 detoxification system might be impaired in spontaneously hypertensive rat (SHR). To verify this, we measured the activities of GPx, CAT, and H_2O_2 level in the kidneys of 4, 6, 8, 12 and 16 weeks old SHR, and in age-matched Wistar-Kyoto rats (WKY). mRNA and protein levels of GPx and CAT were also estimated. Systolic blood pressure (SBP) was measured in all the rats over the same period. SBP of SHR was significantly higher at the age of 6, 8, 12 and 16 weeks when compared to age-matched WKY rats. GPx activity was significantly lower in SHR from the age of 8 weeks onwards, whereas there was no difference in its mRNA and protein levels when compared to age-matched WKY rats. CAT activity was significantly higher in SHR from the age of 6 weeks onwards, which also correlated with increases in its mRNA and protein expressions. H_2O_2 levels in SHR however were significantly lower from the age of 8 weeks onwards. In conclusion, it appears that the H_2O_2 detoxifying system is somewhat enhanced in SHR, which might be related to the raised levels of CAT expression and activity. The reason and significance for the lower GPx activity in SHR, and the precise role of these in the development of hypertension however remains unclear.

STUDY OF PROTEIN BIOMARKER FOR DIABETES MELLITUS TYPE 2 AND ROLE OF HIGH DOSE THIAMINE ON THEIR LEVELS

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Background: This research work describes the levels of protein biomarkers specific to diabetes mellitus type 2 and effect of high dose thiamine on these levels. **Methods:** Type 2 diabetic patients, age and sex-matched normal healthy controls were recruited from Sheikh Zayed Hospital, Lahore, Pakistan. Plasma proteins were analysed by 2-D liquid chromatographic system in which samples were initially fractionated by chromatofocusing and the selected fractions were further analysed by reverse-phase chromatography. The proteins which showed variation between test and control samples were identified by MALDI TOF analysis. Analysis of all the samples belonging to the control, placebo and thiamine treated groups were then analyzed for the four proteins which were found to vary, by ELISA. **Results:** Levels of apolipoprotein A-I was found to decrease by -6.4 % while apolipoproetin-E, leptin and C reactive protein (CRP) were found to increase by +802, +218 and +872 %, respectively in the diabetic patients as compared to the controls. The level of CRP decreased by 63% after thiamine therapy as compared to the controls and the placebo while other protein markers did not show a significant change after the therapy. **Conclusion:** Since CRP level variation has been reported in other pathological sates, role of thiamine may have a significant bearing on the prognosis of such diseases.

GENDER SPECIFIC CORRELATION OF INSULIN RESISTANCE WITH ANTHROPOMETRIC INDICES OF OBESITY IN IMPAIRED GLUCOSE TOLERANT AND NEWLY DIAGNOSED PAKISTANI SUBJECTS

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Obesity has been strongly associated with insulin resistance in normoglycemic and type 2 diabetic subjects independent of hyperglycemia. This study was aimed at determining the correlations among anthropometric indices of obesity (waist circumference, waist hip ratio& BMI) with insulin resistance in impaired glucose tolerant (IGT) and newly diagnosed type 2 diabetic subjects. A total number of 508 subjects (male n = 228, female n = 280) of age between 38-75 years were included in the study. All subjects underwent a 75 g oral glucose tolerance test (OGTT) for the diagnosis of diabetes and IGT. Insulin was assessed by Immunoenzymometric assay. Homeostasis model assessment (HOMA-IR) was employed to estimate insulin resistance. Following the WHO cutoffs for Asians, 35% of our sample population was found to be overweight and 65% were obese, 62% had WHR greater than 1. BMI was higher in females while WHR was greater in males. The BMI of the IGT subjects was significantly higher (P<0.05) as compared to the diabetic subjects. Fasting serum insulin concentration and insulin resistance was higher in IGT group as compared to the diabetic group (P<0.05). A significant gender difference (P<0.05) was observed. IR had significant association with BMI in IGT and diabetics (r = 0.467, r = 0.350, P<0.05). In multiple regression analysis when IR was a dependent variable BMI was determinant in IGT group while waist hip ratio was determinant in diabetic subjects p<0.01.

PROGNOSTIC SIGNIFICANCE OF ADMISSION CREATINE KINASE AND ADMISSION TROPONIN T IN PAKISTANI PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Pakistani people belong to a population that has the highest known rate of cardiovascular disease. Combination of markers of myocardial necrosis, such as admission troponin-t(TnT) or troponin-I along with admission-creatine kinase (CK) would be expected to have more prognostic information compared to single marker. In a resource-constrained developing country, the information about these two markers at the time of admission could be extremely important for predicting the prognosis of acute myocardial infarction (AMI). In order to investigate the prognostic significance of admission-CK and admission-TnT in Pakistani patients with AMI and to find out if CK combined with TnT could be more useful in predicting the long-term cardiac event, a prospective cohort study was carried out. One hundred and eighty-six consecutive patients with AMI were included in this study. The relationship between their serum/plasma CK and TnT levels at the time of admission and clinical outcome was investigated over a mean follow-up of 24.12 ± 3.75 months. Admission-CK was found to be associated with subsequent cardiac event and mortality (P-values = 0.01 for cardiac event and 0.044 for mortality). Admission-CK was also mildly associated with time-interval between onset of symptoms to SK-treatment (correlation coefficient 'r' = 0.23). Odds of encountering a cardiac event in AMI patients with above-normal CK levels (adjusted for gender) were 3.46 times higher than the odds in patients with normal CK levels. Similarly, odds of mortality in patients with positive TnT were 4.6 times the odds in patients with negative TnT. The two biochemical markers, CK and TnT, together did not provide any further information about prognosis of the disease. In conclusion, admission CK is a better prognostic marker for subsequent cardiac event, while TnT is a better predictor of mortality over a follow-up of 2 years.

DIABETES DIAGNOSTIC ENZYME "GLUCOSE OXIDASE" HYPERPRODUCTION BY MUTAGENESIS

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Diabetes mellitus is a set of related metabolic disorders and its increasing intensity requires the exact diagnosis. The widely used enzymatic determination requires the key enzyme glucose oxidase. We assessed the hypothesis that glucose oxidase is used in glucose determination in diabetic patients; its enhanced production will be a step forward in diagnostics. Pure culture of *Aspergillus niger* mutated by the gamma irradiation and ethidium bromide treatment and the optimum dose was selected by formulating the kill curve. The mutants were separated and screened by triton X-100 (1%) as colony restrictor and 2-Deoxy-D-glucose (1 mg mL^{-1}) as selective marker. The potential mutants G-80-A, G-80-B, G-80-C, EB-150-A, EB-150-B, EB-150-C, EB-150-D, and EB-150-E were analyzed and compared for the enzyme diffusion zone test. Wild type zone was recorded as 9 mm along with G-80-A: 26mm and EB-150-E: 19mm. The glucose oxidase analysis for wild type was 100% while mutants G-80-A and EB-150-E resulted in 459% & 260% increase in activity respectively. In conclusion the mutagenesis of *Aspergillus niger* resulted in mutants with far greater activity of the clinically important enzyme and using these mutants for the greater production of the enzyme can combat its extreme superior utilization.

IDENTIFICATION AND MOLECULAR CHARACTERIZATION OF PROTEIN PROFILE IN THE DIABETIC HYPERTENSIVE NEPHROPATHY

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The objectives of the present research work are to study the biochemical parameters and levels of protein biomarkers affecting to hypertensive diabetic nephropathy in the Pakistani population. 100 hypertensive nephropathic diabetic patients and 50 age, sex-matched normal healthy controls were recruited from Sheikh Zayed Hospital, Lahore, Pakistan. Individuals were equally divided into three different groups, group A was control, group B was diabetic hypertensive with nephropathy and group C was diabetic hypertensive without nephropathy. Blood and 24hrs urine were collected and stored for further analysis. Biochemical parameters related to the hypertensive diabetic nephropathy and specific proteins markers were analysed by 2-D liquid chromatographic system followed by mass spectrometric standard referred protocols. The proteins which showed variation between test and control samples were identified by MALDI TOF analysis. The biochemical data showed significantly higher in values of fasting blood sugar, diastolic and systolic blood pressure, total serum and urinary proteins in the diabetic groups with/without hypertensive nephropathy as compared to control in group A. The levels of proteins act as biomarker like microalbuminurea are the most significant in the urine samples of hypertensive nephropathy group B as compared to other groups A and C. Prevalence of proteins in diabetic hypertensive with nephropathy is higher as compared to normal without nephropathy patients in the Pakistani population.

CARDIOVASCULAR RISK MARKERS AMONG TYPE 2 DIABETES MELLITUS PATIENTS OF DIFFERENT AGES

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Type 2 diabetes mellitus (T2DM) is a complex metabolic syndrome, affecting the world population with its growing prevalence. Cardiovascular disease (CVD) is the most serious complication of T2DM which is well documented and considered to be the major cause of morbidity and mortality. CVD accounts for up to 80% of deaths among type 2 diabetic patients. Type 2 diabetic patients carry an array of risk factors like dyslipidemia, hyperglycaemia and insulin resistance which leads to an accelerated probability of CVD. One of the areas of major concern in the clinical management of T2DM is to reduce the risk of CVD. The key aim of this study is to analyse the various biochemical parameters and inflammatory mediators including C-reactive protein (CRP), interleukine-6 (IL-6), tumor necrosis factor (TNF-α), fatty acid binding protein (FABP) in T2DM patients, which will possibly provide key insights to the understanding of CVD in T2DM. Since the accelerated rate of atherosclerosis and CVD in T2DM is likely to be multi-factorial, there is an urgent call for consideration of different therapeutic approaches. This study will assist in the development of potential clinical strategies for the prevention and management of CVD in a high risk population. It is hypothesised that the results of this study can also be used to assess the CVD risk which will reduce the CVD related mortality rates among type 2 diabetic patients.

PROTEINURIA AND GLOMERULAR FILTRATION RATE AS MARKERS FOR OBESITY RELATED GLOMERULOPATHY

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The increase in number of individuals with obesity have increased worldwide. This was associated with emergence of new renal pathology (Obesity related glomerulapathy). Importantly this may occur in individual with and without diabetes. Diabetic nephropathy and obesity-related glomerulopathy are both associated with presence of proteinuria. The reduction in estimated Glomerular filtration rate (eGFR) may occur in diabetic nephropathy and Obesity-related glomerulapthy in the absence of proteinuria. Bariatric surgery and weight loss through dieting are both associated with improvements in insulin sensitivity and both have been reported to be associated with improvement in renal function. Previously we reported that bariaric surgery in type 2 diabetes was associated with significant improvement in GFR and dipstick testing was negative for protein and normal albumin creatinine ratio. Furthermore, we have shown that weight loss is also associated with significant improvement in all parameters of renal function in non diabetic individuals. Insulin resistance is cornerstone in the pathogenesis of Obesity-related glomerulopathy. We suggest that the use of GFR and measurement of urinary protein and albumin should be part of assessment of all obese individuals. Future studies will be needed to assess how early intervention may prevent the progress to end stage renal failure.

SIMPLE AND REGULAR FULL BLOOD COUNT IS AN EXCELLENT MARKER FOR COMMUNITY APPROACH FOR EARLY, SIMPLE, AND RAPID DETECTION OF ANAEMIA DUE TO DIABETIC NEPHROPATHY: IMPACT ON PROGRESSION TO END STAGE RENAL DISEASE

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Anaemia is common among patients with chronic kidney disease (CKD) and diabetes. It is associated with poor quality of life, increased hospitalization and risk of CVD. Early detection of anaemia due to diabetic nephropathy may improve prognosis. In this study we monitored full blood count in addition to routine renal profile for diabetic individuals in primary care. The aim was to detect early anaemia due to diabetic nephropathy and to prevent progression to end stage renal failure. This was achieved via 1) Small group medical meetings to increase awareness 2) Frequent FBC tests for patients with diabetes in order to facilitate early recognition of anaemia 3) Community sharing of the hospital based renal anaemia management protocol for the prompt, safe, and effective management of diabetic nephropathy anaemia. The outcome showed 3 fold increase in numbers of individuals diagnosed with anaemia, early intervention with iron and Epo did slow the progression of CKD to End Stage Renal Failure in 7 % of patients and hence their Qol improved as they remained dialysis free. Moreover, anaemia correction was associated with increased energy and improved socio economical productivity. Additionally, fewer patients were hospitalized for CVD events than patient who failed to adhere to anaemia management program.

N-Terminal Pro-BNP In Acute Coronary Syndrome Patients With ST Elevation Versus Non ST Elevation

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Aim: To investigate the differences in the secretion of NT-proBNP and conventional cardiac markers in patients with STE-ACS vs. NSTE-ACS as a trial to solve the dilemma of the early detection of myocardial ischemia in NSTE-ACS. **Design**: Prospective case control hospital based study. **Setting**: King Fahed Specialist Hospital, Buraidah, KSA. **Patients and methods:** Sixty two patients with acute coronary syndrome (ACS) divided into 2 groups according to ECG : group1 with elevated ST segment in ECG (STE-ACS) and group 2 with non elevated ST segment (NSTE-ACS).Twenty healthy subjects with matched age and sex were enrolled as control group in this study. In the sera of all subjects, levels of NT –proBNP, CK-MB and troponin- T were measured by different kits. **Results:** CK-MB and Tn-T were both significantly higher in STE-ACS patients compared with NSTE-ACS patients. Conversely, NT-proBNP was significantly higher in NSTE-ACS patients than STE-ACS especially within 4 hours from onset of chest pain. This suggested a larger ischemic insult despite the smaller extent of myocardial necrosis compared with STE-ACS patients. Comparison between sensitivity and specificity of NT-proBNP, Tn-T and CK-MB levels by ROC curves revealed a marked difference of area under the curves with higher sensitivity and specificity of NT-proBNP in NSTE-ACS patients. **Conclusions**: NT-proBNP will be a sensitive marker in the early phase of NSTE-ACS patients as compared with conventional markers of myocardial damage.

SUBJECTIVE SLEEP DURATION AND QUALITY INFLUENCE DIET COMPOSITION, ADIPOCYTOKINE AND GHRELIN LEVELS IN TEEN-AGE GIRLS

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Aim: Understanding the interplay between sleep duration and quality, diet and hormones of obesity, may help design effective lifestyle intervention strategies. Here we studied such associations in lean and obese teen-aged Saudi girls. **Methods:** In this cross-sectional observational study, 126 girls (62 lean and 64 obese) aged 14 -18 years (16.5 ± 1.5) were evaluated. A general questionnaire, which included sleep and diet questions, was obtained and anthropometric measurements and overnight fasting blood samples for determination of glucose, lipid profile and serum levels of leptin, adiponectin, resistin and ghrelin were collected. **Results:** Subjects that slept < 5 hours/day showed a higher percent of carbohydrate intake (p= 0.04) than those who slept >7 hours/day. Adiponectin levels were higher in the lean group and increased in proportion to hours of sleep. Ghrelin had an inverse association (p = 0.04) while resistin levels were directly proportional to sleep duration. **Conclusion:** The duration and quality of sleep influence diet and the circulating levels of adipocytokines and ghrelin in adolescent girls. Long and uninterrupted sleeps were associated with a better diet and a more favorable hormonal profile.

ZINC SUPPLEMENTATION LIMITS THE CARDIOVASCULAR COMPLICATIONS IN STREPTOZOTOCIN-INDUCED DIABETES IN RATS

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Diabetes is one of most prevalent diseases that is now regarded as the strongest risk factor for cardiovascular diseases. This study aimed to investigate whether combination of zinc sulfate with glibenclamide prevent or delay cardiovascular complications. Diabetes was induced in rats by a single intraperitoneal injection of streptozotocin (STZ, 40 mg kg^{-1}). After 45 days, diabetic group showed cardiovascular complications manifested by significant elevations of troponin-I (0.24 ±0.03 ng ml^{-1} Vs. 0.023 ±0.001, p<0.001) as well as cardiac enzymes. Total cholesterol, LDL-C and triglycerides were significantly increased compared to non-diabetic group. Diabetic group showed impaired oxidative status manifested by a significant elevation of lipid peroxides, and reductions of glutathione and L-ascorbic acid. Serum levels of TNF-α were significantly increased compared to non-diabetic group (236.5±16.2 ng ml^{-1} Vs. 169.7±2.9,p<0.001). Nitric oxide (NO) and vascular endothelial growth factor (VEGF) were markedly higher indicating endothelial dysfunction and disturbance of angiogenesis. Treatment with glibenclamide (600 µg kg^{-1}, i.p) resulted in an improvement in most of the deviated biochemical parameters. However, combination of glibenclamide with zinc sulfate (20 mg kg^{-1}, i.p) showed more pronounced hypoglycemic effect and a significant improvement in cardiac function as compared to glibenclamide alone treated group. Moreover, LDL-C was significantly decreased by the combination (34.46±2.7 mg dl^{-1} Vs. 49.35±4.1, p<0.01). Oxidative stress markers were improved by the combination. Serum levels of TNF-α, NO and VEGF were significantly reduced by the combination. These findings indicate that combination of zinc with glibenclamide may potentiate hypoglycemic effect of glibenclamide and limit the diabetic complications.

THE IMPACT OF STRESS MANAGEMENT INTERVENTION ON THE QUALITY OF LIFE OF SAUDI FEMALE PATIENTS WITH METABOLIC SYNDROME AT AL-SOLIMANIA PRIMARY HEALTH CARE CENTER

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Metabolic syndrome (MS) is a term which refers to a combination of medical disorders that are associated with a higher risk for cardiovascular disease and diabetes. It is known that MS has affected a large number of people around the world. The global statistics shows that approximately a quarter of adult populations suffer from this clinical entity .According to various studies the prevalence of MS in general population in the United States, Saudi Arabia, and Turkey are 24%, 39.3%, and 33.4%, respectively. Studies have demonstrated that management of stress improves specific aspects of health. Stress management was shown to be capable of reducing the risk of heart attack, elevated blood pressure, elevated blood sugar, elevated cholesterol levels and consequently improve quality of life. The aim is to examine impact of stress management intervention on the quality of life of Saudi females with MS. 20 Saudi females with MS, whose 40 years and above. Independent, diagnosed with MS (diabetes, hypertension, obesit & regularly attending the primary health care center at Al-Solimania region. Data was gathered through personal interview randomly using demographic data. Scale of comprehensive quality of life scale-adult fifth edition (com Qol-A5). Subjects divided into 2 groups, quality of life scale & the following parameters were determined before and after the intervention: body mass index (BMI), waist-hip ratio, blood pressure, fasting blood sugar, Glycosylated hemoglobin (HbA1c), and lipid profile. Stress management intervention tools that suit the culture according to the primary health care policy will be applied for each group. There was a significant decrease observed in BMI, waist-hip ratio ,fasting blood sugar, systolic blood pressure & improve quality of life.

ANTIHYPERLIPIDEMIC ACTIVITY OF 3-HYDROXYMETHYL XYLITOL, A NOVEL ANTIDIABETIC COMPOUND ISOLATED FROM *CASEARIA ESCULENTA* (ROXB.) ROOT, IN STREPTOZOTOCIN-DIABETIC RATS

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Introduction: Diabetes mellitus is a major risk factor for the development of cardiovascular complications and cardiovascular disease. **Hypothesis**: The objective of the study was to investigate the role of 3-hydroxymethyl xylitol (3-HMX), a novel antidiabetic compound, isolated from Casearia esculenta root, on lipid profiles in the plasma and tissues (liver, kidney, heart and brain) of streptozotocin (STZ) diabetic rats. **Methods**: Adult male albino rats of Wistar strain, weighing 180–200 g, were induced diabetes by administration of streptozotocin (40 mg/kg BW) intraperitoneally. The normal and diabetic rats were treated with 3-HMX (40 mg/kg BW) for 45 days. **Results and Conclusions**: Diabetic rats had an elevation in the levels of total cholesterol (TC), triacylglycerol (TG), free fatty acids (FFA), phospholipids (PL), low density lipoprotein (LDL-C) and very low density lipoprotein (VLDL-C) and decreased the level of high density lipoprotein (HDL-C) in plasma. Tissues of total cholesterol (TC), triacylglycerol (TG), free fatty acids (FFA) and phospholipids (PL) were increased in diabetic rats and on treatment with 3-HMX or glibenclamide brought lipid profiles towards normalcy. Thus, the result of this study clearly shows the 3-hydroxymethyl xylitol possesses antihyperlipidemic properties.

A PREPRANDIAL AND POSTPRANDIAL PLASMA LEVELS OF GHRELIN HORMONE IN LEAN, OVERWEIGHT AND OBESE SAUDI FEMALES

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Ghrelin is a novel gastrointestinal peptide hormone isolated from human and rat stomach. Ghrelin administration stimulates growth hormone secretion but also causes weight gain by increasing food intake and reducing fat utilization in rodents. This study aims to determine the plasma level of ghrelin under basal condition and in response to a standard meal and to elucidate the relationship between this peptide and anthropometric measures. Body mass index (BMI), anthropometric measurements were calculated and Plasma ghrelin concentrations were determined in 122 obese, overweight and lean Saudi Females before and an hour after breakfast. Fasting ghrelin was significantly higher in lean than in obese and overweight subjects and fall after eating in the lean group. There was slight insignificant reduction in circulating ghrelin of the obese and overweight group. Ghrelin levels were negatively correlated with BMI in obese, overweight and lean subjects. Obese subjects do not exhibit the decline in plasma ghrelin seen after a meal in the lean; the lack of suppression following a meal in obese subjects could lead to increased food consumption and suggest that ghrelin may be involved in the pathphysiology of obesity.

DIABETIC PATIENTS ARE THREATENED BY FOUR NOVEL *BLA* OXA-51-LIKE GENES OF *ACINETOBACTER BAUMANNII* IN SAUDI ARABIA HOSPITALS

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Introduction: Saudi Arabia is one of the top five countries in the world with the highest prevalence of diabetes in the adult population. Patient with Diabetes mellitus are 10 time more likely to develop multi-resistance *Acinetobacter baumannii* than the rest of population. OXA-51-like β-lactamases are present in all isolates of *A. baumannii*. Multi-drug resistance (MDR) has becoming a major problem facing clinicians in hospitals worldwide and carbapenems are the drug of choice for treating infections caused by *A. baumannii*. The aim of this study is to find out the potential risk that may threaten diabetics by the new clones of *A. baumannii* carrying novel genes of OXA-51-like in Saudi Arabia. **Methods:** Thirty-eight clinical isolates from diabetes and non diabetes were collected from Eastern Saudi hospitals and identified by 16S-23S-rRNA and the presence of a *bla*OXA-51-like gene. Susceptibility to antimicrobials was determined. Bacterial clones were analyzed by Pulsed Field Gel Electrophoresis (PFGE). Bacterial growth was measured in media containing increasing glucose concentration. **Results:** The prevalence of carbapenem resistance was investigated in diabetic patients. The representative isolates of *A. baumannii* were found to possess common gene variants designated OXA-90, OXA-130, OXA-131 and OXA-132. These novel genes, as well as another six of *bla*OXA-51-like genes are probably associated with developing MDR *A. baumannii* in diabetics. **Conclusions:** A new risk factor may threaten diabetic patients with emergence of four new strains of *A. baumannii* harbouring the OXA-51-like gene. The four novel genes have been reported and deposited in the GenBank nucleotide database under unique accession numbers.

INSULIN RESISTANCE AND ATHEROSCLEROSIS IN CHRONIC RENAL FAILURE: ROLE OF ADMA AND PROTECTIVE EFFECT OF CATECHIN, VITAMIN E AND VITAMIN C TREATMENT IN AGED RATS

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Introduction: Atherosclerosis and IR constitute major risk factors for cardiovascular mortality in elderly with chronic kidney disease. **Objectives**: To investigate the impact of catechin, vitamins E&C supplementation on insulin sensitivity, redox state, ADMA, nitrate and nitrite (NO_2^-/NO_3^-) levels and histological picture of heart and large blood vessels of aged rats with chronic renal failure (CRF). **Methods**: 40 male Wister rats; group I (8-12 wks old), group II,III, and IV (1.5-2 years old). Group I&II were untreated control. Group III (CRF- untreated)& group IV (CRF- treated with Catechin100mg/kg/day, Vit. E 400 mg/kg food and, Vit. C 500 mg/kg food enriched diet) for 12 weeks. Serum insulin, glucose, (HOMA-IR),lipid profile, kidney functions , systolic blood pressure (BP), ADMA,NO_2^-, NO_3^-, MDA, GSH levels and serum activities of SOD and CAT were investigated. Heart muscle, aortic ,carotid artery tissues were examined histopathologically. **Results:** Aging in rats is associated with hyperinsulinemia, hyperlipidemia, IR, increased MDA, ADMA, and BP, but decreased antioxidant capacity and NO_2^-/NO_3^- levels. CRF exaggerated all these findings and caused thickened intima of carotid arteries and myocardial hypertrophy. Treatment with catechin, vitamins E &C increases the antioxidant capacity and NO_2^-/NO_3^- production but, decreases MDA, ADMA and BP levels. It keeps insulin sensitivity and normal intima/media thickness of carotid and aortic arteries. **Conclusion**: Decreased nitric oxide availability due to ADMA accumulation may be responsible for IR and associated atherosclerotic changes in aged rats with CRF. Catechin, vitamins E& C supplementation may moderate oxidative stress of renal failure, prevent ADMA accumulation, and counteract IR and atherosclerotic changes in the elderly.

RETINOL BINDING PROTEIN-4 IS ASSOCIATED WITH TNF-α AND NOT INSULIN RESISTANCE IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND CORONARY HEART DISEASE

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We studied the association between RBP4 and various markers related to insulin resistance and diabetic complications as well as inflammatory markers in Saudi population suffering from type 2 diabetes and coronary heart disease. Patients with type 2 diabetes were divided into 3 groups according to the type of treatment and involvement of coronary artery disease. Serum TNF-α, insulin, CRP, resistin, leptin and adiponectin were analysed in all samples. RBP4 plasma levels increased significantly in the group of diabetic subjects treated with oral hypoglycemic agents and diabetic patients with coronary heart disease (30.2 ± 11.8; 33.4 ± 13.6 respectively), while there was no significant change in the other group for diabetic subjects on low-carbohydrate diet (25.1 ± 10.9) compared to control group (22.6 ± 9.5). RPB4 levels were positively correlated with TNF-α in the group of diabetic subjects on oral hypoglycemic agents and diabetic patients with coronary heart disease (r =0.52, P < 0.05; r =0.58, P < 0.05 respectively). No correlations were found between RBP4 level and insulin resistance in all studied groups. Our findings suggest that serum RBP4 levels is associated with pro-inflammatory cytokine (TNF-α) and is not associated with insulin resistance among patients with type 2 diabetes and coronary heart disease.

RELATIONSHIP BETWEEN RESISTIN AND APAI-1 LEVELS WITH INSULIN RESISTANCE IN SAUDI CHILDREN

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Association of resistin with insulin resistance (IR) in human is still controversial and few studies have investigated the association of plasminogen activator inhibitor-1(PAI-1) with IR in children. The purpose of our study was to evaluate serum levels of resistin and active PAI-1 in Saudi children and their association with the various obesity related complications. In this cross sectional study, 73 boys and 77 girls with varying BMI were recruited. They were assessed for anthropometric measures and fasting serum levels of glucose, insulin, lipid profile, resistin, Angiotensin II (ANG II) and aPAI-1. Resistin was positively correlated with hips (r=0.33, p< 0.01), waist (r=0.23, p< 0.05) and BMI (r=0.33, p<0.01). While aPAI-1 was positively correlated with both total and LDL cholesterol (r =0.24; p< 0.01; r = 0.24, p< 0.01 respectively), triglycerides (r=0.2, p< 0.05), HOMA-IR (r=0.26, p<0.01) and insulin (r=0.26, p<0.01). These findings show that resistin is not correlated with IR and further studies are needed to explore the role of resistin especially in childhood obesity. On the other hand, increased levels of PAI-1 may contribute to the risk of cardiovascular diseases related to obesity and insulin resistance in children. The observed gender related differences in the association between resistin, aPAI-1 with obesity markers and insulin resistance could be attributed to sexual dimorphism in body fat distribution.

ROLE OF HYPERLEPTINEMIA IN HYPERTENSION

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Background and Objective: Hyperleptinemia is associated with risk factors of hypertension(HTN) including increased sympathetic activity, obesity, insulin resistance, renal pathology and vascular inflammation. The objective of this work was to determine whether any relationship exists between hyperleptinemia and HTN. **Subjects And Methods:** It was a case control study of 6 months duration, carried out at Shifa College of Medicine and Shifa International Hospital Islamabad. We studied 128 male subjects, 64 with HTN and 64 without HTN. Leptin levels were measured by enzyme linked immunosorbent assay (ELISA) technique.The relationship between leptin (LEP), body mass index (BMI), random blood sugar (RBS), smoking, and cholesterol levels with blood pressure were assessed. **Results:** Patients with HTN versus patients without HTN were smokers (39% to 10%), had a higher body mass index (27.04 +/- 0.43 to 24.31 +/- 0.375 kg/m2) , RBS (167 +/- 7.32 to 132 +/-7.6mg/dl), total cholesterol (160+/- 4.72 to 158 +/- 3.74 mg/dl) and LEP (52.49 +/- 5.32 to 20.65 +/- 3.5 ng/ml) levels. In univariate analysis smoking, obesity, hyperglycemia and hyperleptinemia (with p values of 0.001), whereas in multivariate analysis smoking , hyperglycemia and hyperleptinemia (with p values of 0.016, 0.006 and 0.001 respectively) were risk factors for HTN. The present study therefore indicated that serum leptin levels are significantly higher in the patients of HTN as compared to the control group. Moreover hyperleptinemia showed highest values of odds ratio in both univariate and multivariate analysis, thereby indicating that it may be a stronger risk factor than smoking, obesity and hyperglycemia, for HTN. **Conclusions:** We suggest that hyperleptinemia may have a major role in the development and progression of HTN, and it could be considered as an independent risk factor for HTN and cardiovascular disease.

RELATIONSHIP OF SERUM LEPTIN LEVELS WITH BODY MASS INDEX AND GENDER

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Objective: Hyperleptinemia may be the underlying cause of various obesity related disorders including insulin resistance, hypertension and hyperlipidemia. The objective of the study was therefore, to probe the relationship between hyperleptinemia, obesity and gender which may be helpful to solve various obesity related disorders. **Patients and Methods:** This observational study was carried out at Shifa college of Medicine in a duration of six months. Serum leptin levels of ninety five healthy male and female individuals were measured. Height and weight of the subjects was recorded and BMI was then calculated as weight (kg) divided by height (m²). Leptin levels were measured by DRG Leptin (sandwich) ELISA EIA-2395. **Results**: The results of the our study have revealed that serum leptin levels are significantly higher in the female group (25.37 ± 22.82 ng/ml) as compared to the male group (11.12 ± 10.68 ηg/ml). Leptin levels were also found to be higher in the overweight and obese (BMI ≥ 25kg /m²) individuals (26.78 ± 19.13 ng/ml) as compared to the normal weight (BMI < 25kg/m²) subjects (6.30 ± 5.06 ng/ml). Moreover leptin levels were also compared between normal and obese individuals in male and female subjects separately and results were found to be statistically significant (P value < 0.05). **Conclusions:** The present study indicated that gender and BMI are the major determinants of serum leptin levels. Serum leptin levels of females were two times higher as compared to males. Overweight and obese individuals showed higher serum leptin levels as compared to lean and normal weight individuals.

OXIDATIVE STRESS IN RATS FED ON HIGH CHOLESTEROL DIET: ROLE OF FLAXSEED OIL AND α- LIPOIC ACID

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Hypercholesterolemia associated with increase production of reactive oxygen species. Moreover supplementation of alpha lipoic acid (ALA) increases cellular antioxidants. The polyunsaturated fatty acids in flaxseed oil (FO) are liable to lipids peroxidation. This study was conducted to assess effects of ALA and FO administration on oxidative stress status in serum and liver of rat fed on high cholesterol diet (HCD). Male Wister albino rats in control group were fed on standard diet, while in another groups the rats were received HCD alone or in addition to FO at dose (1 g/kg), ALA at dose (20 mg/kg), and combination between them. In our work hypercholesterolemia in rat was demonstrated by significant elevation of serum total cholesterol as a result of HCD feeding. Glutathione peroxidase activity was markedly higher in rats received HCD in comparison with FO and ALA treatment. Moreover, reduced glutathione was significantly decreased by cholesterol feeding while its level is maintained by supplementation of rats with either FO or ALA. In the treated groups there is a considerable decline of malondialdehyde concentration compared with HCD feeding. Furthermore, the treatments cause restoration of protein thiols level while protein carbonyl formation is minimized in comparison with HCD. Oxidative stress in hypercholesterolemia is decreased by administration of either ALA or FO. The greater reduction of oxidative stress was exerted by combination between them. It is concluded that supplementation with antioxidants is necessary.during the cholesterol lowering therapy especially with oils rich in polyunsaturated fatty acids.

HIGH SENSITIVITY C REACTIVE PROTEIN AND LIPOPROTEIN(A) IN THE ASSESSMENT OF THE PRESENCE, DIFFUSENESS, AND SEVERITY OF CORONARY ARTERY DISEASE IN SAUDI POPULATION

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Objectives: To determine high sensitivity C reactive protein (hsCRP) and lipoprotein(a) [Lp(a)] levels in Saudi patients with angiographically defined coronary artery disease and to see its relationship with its severity and diffuseness. **Methods:** This cross sectional study was carried out at King Khalid University Hospital, Riyadh. One hundred and forty-seven individuals with chronic stable coronary artery disease (CAD) and 49 healthy individuals matched for age and body mass index were studied. Among CAD patients, 133 underwent angiography. Blood samples were analyzed for total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL), Lp(a) and hsCRP. **Results:** Coronary artery disease patients had higher Lp(a) (25.78±25.09mg/dl versus 14.57±11.81 mg/dl, *p*=0.0030) and hsCRP (5.0 ± 4.4 verses 2.7 ± 2.7 mg/L, p=0.0166) levels than controls. Patients without stenosis (10.97±8.06mg/dl) and one vessel involvement (19.67±17.33mg/dl) had significantly lower levels of Lp(a) compared to double (31.88±32.17mg/dl) and triple (29.70±28.12mg/dl) vessel disease. Lp(a) levels were correlated significantly with coronary vessel score (r=0.234, *p*=0.033) and Gensini score of CAD severity (r=0.256, *p*=0.02) while hsCRP did not show such correlation. Smoking (odds ratio [OR]: 1.86; 95% confidence interval [CI]: 1.020-2.510; *p*=0.04), TG levels (OR: 2.04; 95% CI: 1.251-4.932; *p*=0.03) and Lp(a) levels (OR: 1.56; 95% CI: 1.033-3.687; *p*=0.025) significantly predicted CAD severity. **Conclusion:** Lipoprotein(a) and hsCRP are markers of the presence of coronary artery disease in Saudi population. However, only Lp(a) but not hsCRP levels are associated with severity and diffuse blockage of the coronary vessels**.**

FECAL MPO, LACTOFERRIN, AND SERUM CRP ARE EFFECTIVE BIOMARKERS IN ASSESSING DISEASE SEVERITY AND RESPONSE TO TREATMENT IN ULCERATIVE COLITIS

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Aim: To study the role of Fecal Myeloperoxidase (FMPO) in assessing disease activity and response to therapy as an outpatient in a non-invasive manner. **Patients and methods:** Consecutive patients with IUC attending the Gastroenterology services of a tertiary Care referral institution from July 2005 to September 2006 were prospectively studied . Patients more than 60 years, with prior colectomy, or toxic mega colon were excluded. Supernatants of the stool samples in saline were stored at -20°C for estimation of MPO. The stool samples of 54 healthy age matched controls were stored for estimation of MPO. Subjects with history of any abnormal bowel pattern in the preceding one month were not included as controls. Patients were re-evaluated after 4-6 months of treatment. Repeat sigmoidoscopy was done and MPO was re-estimated. **Results** Fecal MPO was measured in 54 age matched healthy controls (36 males)and 55 IUC patients(30 males) Mean MPO levels were significantly elevated (0.723±0.865) in 85.45% (47/55) patients in contrast to control group who had mean MPO levels of 0.099±0.977 (p<0.001).Cases with endoscopically severe disease (Grade IV) had higher FMPO levels than those with Grade I-III involvement, which however, did not reach statistical significance .There was no significant correlation observed between MPO and endoscopic extent,(P=0.71) and histological scores of activity and chronicity (P=0.648). **Follow-up**: 37 patients were re-evaluated between 4 to 6 months after start of treatment. All patients had clinical response to therapy and there was significant reduction in Mayo score (7.10±2.19 to 2.8±1.5, p=0.00) Mean fecal MPO reduced significantly on follow up from 1.0061±1.03 to 0.5365±0.8139, (p=0.001) **Conclusion:** Fecal MPO is effective in assessing disease activity and response to treatment in patients with ulcerative colitis.

RESEARCH IN BIO- AND GENETIC MARKERS OF MULTIFACTORIAL DISORDERS- PROS AND CONS

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Most chronic diseases of later life are complex multi-factorial disorders and are the most frequent cause of morbidity and mortality in human population. These disorders have a genetic basis and are polygenic, but the disease development is frequently coupled to the influence of environmental factors. Most genes associated with multi-factorial disorders have low penetrance, and the individuals with disease-related genes do not necessarily succumb to disease under favorable lifestyle and environment. Hence, there is the possibility to delay and even to avoid the disease development in genetically susceptible individuals, by identifying them pre-symptomatically. Using such an approach the development of cardiovascular disease and cancer has been significantly reduced in several populations. However, there are several drawbacks in this field of research. Firstly a large population group is needed for these studies; secondly, the selection of controls is not simple; thirdly, the marker most strongly associated, is always identified in certain percent of the healthy controls; fourthly, the markers frequency shows variations in different ethnic groups; fifthly, these investigations are expensive. However, there is still extensive research funded in this field and there is a need for more funds. We have investigated bio- and genetic markers of diabetes mellitus, hypertension, cardiovascular disease and obesity in Saudis and using our experience, this paper will present and discuss the pros and cons of research in the field of markers of multi-factorial disorders. The major aim of this presentation will be to highlight the importance of this research and the care necessary in interpreting the results.

N-ACETYLCYSTEINE AND COENZYME Q_{10} IMPROVE MYOCARDIAL ENERGY EXPENDITURE, OXIDATIVE STRESS, AND ENERGY METABOLISM IN CARBON TETRACHLORIDE INTOXICATED RATS

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The present work is aimed to evaluate the protective effect of N-acetyl cystiene (NAC), coenzyme Q_{10} (CoQ_{10}), and their combination against carbon tetrachloride (CCl_4)-induced cardiotoxicity in rats. CCl_4 treatment significantly elevated the levels of cardiac oxidative stress biomarkers including nitric oxide (NO) and malondialdehyde (MDA). A concomitant decrease in the level of reduced glutathione and the activity of membrane bound enzyme, calcium-adenosine triphosphatase were observed in the hearts of rats exposed to CCl_4 compared to values in normal group. Quantitative analysis of myocardial energy metabolism revealed a significant decrease in the glucose content coupled with a depletion in the activities of myocardial glycolytic enzymes as hexokinase (HK), phosphofructokinase (PFK) and lactate dehydrogenase (LDH) after CCl_4 treatment. In addition, a significant elevation in myocardial hydroxyproline level was observed in CCl_4 intoxicated rats indicating interstitial collagen accumulation. Pretreatment with either NAC , CoQ_{10} or their combination successively alleviated the alterations in oxidative stress and antioxidant markers, as well as effectively up-regulated the decrease in the energetic biomarkers in the heart of CCl_4-treated rats. Moreover, these antioxidants markedly reduced myocardial hydroxyproline level versus that of CCl_4-intoxicated animals. In conclusion, the present results illustrated that the prophylactic use of the current antioxidant resulted in a remarkable cardioprotective effect against CCl_4 induced myocardial damage, which suggest that they may candidates as prophylactic agents against different cardio-toxins.

DIAZEPAM POTENTIATES THE PROTECTIVE EFFECT OF SIMVASTATIN AGAINST PSYCHOLOGICAL STRESS- ENHANCEMENT OF DOXORUBICIN-INDUCED CARDIOMYOPATHY

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Critically ill patients as cancer patients usually suffer from stress, which is known to be implicated in the deterioration of their condition and the progression of other various disorders. Doxorubicin (DOX) is a highly effective antitumor, however its usefulness is limited by the risk of developing cardiomyopathy. The present study was undertaken to investigate the role of psychological stress in enhancement of DOX cardiotoxicity, and the possible cardioprotective effect of simvastatin (SIM) and diazepam (DIZ) against such toxicity. DOX was administered to rats in 6 equal injections over a period of 2 weeks (cumulative dose, 15 mg/kg). Rats were exposed to stress-induced box paradigm 3 times during the period of DOX treatment (cumulative 30 volts for 3 h). Protection from stress-enhancement of DOX oxidative cardiac injury was assessed by administration of either (1) SIM (cumulative dose, 60 mg /kg) in 12 equal oral doses over a period of 4 weeks (2 weeks before and 2 weeks concurrent with DOX) ;or (2)SIM+ DIZ (0.1 mg /kg, i.p.) prior to each stress exposure. DOX treatment altered most of electrocardiograph parameters, and reduced body and heart weights. It also increased myocardial lipid peroxides, mortality% , and reduced myocardial glutathione (GSH), glutathione-S-transferase (GST), and DT-diaphorase activities. Psychological stress enhanced myocardial damage induced by DOX. Pretreatment with SIM or SIM+DIZ ameliorated cardiomyopathic changes-induced from stress-enhancement of DOX oxidative cardiac damage. These results demonstrate the role of psychological stress in enhancement of DOX cardiomyopathy and the qualitative differences in the protection provided by simvastatin and its combination with diazepam.

METHYLENE TETRAHYDROFOLATE REDUCTASE AND ANGIOTENSINOGEN CONVERTING ENZYME GENE POLYMORPHISMS RELATED TO OVERWEIGHT/OBESITY AMONG SAUDI SUBJECTS FROM QASSIM REGION

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Background. This work was planned to check for the associations of polymorphisms related to methylenetetrahydrofolate reductase (MTHFR) and angiotensinogen converting enzyme (ACE) genes with overweight/obesity among Saudi subjects from Qassim region. **Methods**. This work included 130 subjects having overweight or obesity and 111 normal controls. Their age ranged between 18-40 years. Their DNA was analyzed for polymorphisms of MTHFR; 677C/T and 1298 A/C and ACE; I/D genes using real-time PCR. **Results.** Genotype and allele frequencies of studied polymorphisms in cases of overweight and/or obesity showed no significant statistical difference compared to that of controls. However, on analysis of body mass index (BMI), cases showed higher mean ± SD values –although nonsignificant- among those carrying the mutant MTHFR 677 T allele (CT+TT vs. CC, 30.7±4.5 vs. 29.9±4.9), 1298 C allele (AC+CC vs. AA, 29.9±4.1 vs. 29.7± 5.5) and ACE D allele (ID+DD vs. II, 30.0±5.1 vs. 29.1 ± 2.8). In addition controls having the DD and ID genotypes showed higher statistically significant values of BMI than those of the II genotype (22.0 ± 1.9, 21.7 ± 2.6 and 19.5 ± 2.3 respectively, p<0.05). **Conclusion.** There is no solid association of polymorphisms related to MTHFR and ACE genes with non-complicated overweight or obesity. Among subjects from Qassim region.

THE EFFECT OF ATTITUDE TOWARD PHYSICAL ACTIVITY ON BLOOD SUGAR HEMOGLOBIN LEVELS (HBA1C) AND BODY MASS INDEX FOR MIDDLE SCHOOLS STUDENTS IN RIYADH, SAUDI ARABIA

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Aims: The study aim is to know the effect of attitude toward physical activity on blood sugar hemoglobin and the body mass index for middle schools students Riyadh. **Methods:** The study uses the descriptive method (co – relatives). *Samples of the study*: The Sample of the study was collected longitudinally from middle schools students in Riyadh, Saudi Arabia. Participants were 654 students from Riyadh school district, they were divided into two groups after applying the questionnaire for attitudes toward physical activity, the first group who have a positive attitude toward physical activity, the second group who have negative attitude toward physical activity. Both groups were then tested for HbA1c and measured for Body Mass Index. **Results:** HBAIC for students who have positive attitude toward physical activity is less than the those who have a negative attitude toward physical activity. Body mass index of students who have positive attitude toward physical activity is less than those who have a negative attitude toward physical activity. **Recommendations:** Working to develop positive attitudes toward physical activity among students. Students should engage more in physical activity programs. The necessity of having hemoglobin sugar blood test. Measuring body weight is an indication of students health.

GENETIC PROGNOSTIC BIOMARKERS IN SAUDI COHORT IN RELATION WITH HBV

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HLA class I & II the integrals components of the immune system that encodes the most polymorphic genes known in vertebrates were detected in this comprehensive study in the Saudi cohort infected with HBV.The study revealed that old age had the most significant impact in chronic carrier patients (60%), on the contrary the chronic active were associated with young patients (70.4%). Therefore we could conclude that young age and male gender (77.8%) were the major determinants of chronic active patients. **The HLA class I** showed that *HLA-A24* was associated with male (p=0.0306513), while *HLA-A68* was associated with female (p=0.0590038). While, we didn't find any alleles in **class II** related to genders. It was found that four alleles in **class I** were absent *(A25, A34, B42 and CW5)* in both subject groups .Further functional studies are needed to understand the basis for these relationship and the link between the genes associated with both viral persistence and with no response to the HBV infection especially for the alleles that were absents. The data of **class II** alleles indicated that *DQB1*03* was significantly associated with HBV chronicity with the percentage of (26.67%, 37.04%), moreover *BW4 and B51* were significantly associated with chronic carrier patients with elevated values of AST enzyme. The normal individuals showed that alleles of **class II** had their expression with a significant values *DRB1*13* (23%), *DQB1*06* (43%), *DQB1*03(7)* (23.33%) compared to the CC & CA patients. It was remarkable that the most frequent alleles were *BW4* 80% and *B51* 60% existed in chronic carrier while one allele only *DQB1*03* had frequency in chronic carrier and chronic active**.**

ASSOCIATION OF ADIPONECTIN GENE POLYMORPHISMS TO METABOLIC PHENOTYPES IN SAUDI POPULATION

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Polymorphisms of adiponectin gene are associated with metabolic phenotypes in different populations. We tested the associations of two most common single nucleotide polymorphisms (SNPs), 45T>G and 276G> T, of adiponectin gene (ADIPOQ) with adiponectin levels and the metabolic phenotypes in Saudi population. A total of 300 normal and 297 T2DM subjects were examined in this cross sectional study. Anthropometric, clinical and biochemical parameters were measured by standard procedures. Adiponectin levels were assayed by ELISA. The SNPs were examined by PCR-RFLP analysis. The genotype distributions of SNP 45T>G were not statistically different between the control and T2DM groups (TT= 0.701 vs. 0.738, TG= 0.268 vs. 0.241, GG= 0.030 vs. 0.20 respectively, p= 0.5, χ2). The SNP 276G> T was not associated with T2DM (GG= 0.410 vs. 0.373, GT= 0.451 vs. 0.478, TT= 0.138 vs. 0.148 respectively, p= 0.6, χ2). Adiponectin levels within the genotypes of both the SNPs (TT, TG, GG for SNP 45T> G & GG, GT, TT for 276G> T) in control and T2DM subjects were not significantly different after multiple regression analysis controlling for age, sex and BMI. On the other hand adiponectin levels were significantly associated with T2DM and other metabolic phenotypes in control and T2DM subjects. Taken together, our data suggest that 45T>G and 276G> T SNPs of ADIPOQ gene are not an important determinants of metabolic phenotypes in the Saudi population. These SNPs either are under linkage disequilibrium with other functional variants and/or influenced by potential modifying factors.

SIGNALING MECHANISMS IN REGULATION OF ABNORMAL VASCULOGENESIS BY TYPE IV COLLAGEN DERIVED ANGIOINHIBITORS

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We identified several endogenous neovascular inhibitor molecules that are released from extracellular matrix (ECM) into the circulating blood of patients. Several of these endogenous circulating molecules were cloned in the laboratory and identified them as inhibitors of angiogenesis (neovascularisation). These endogenous anti-neovascular proteins binding to cell surface integrins and transduce the signalling mechanisms in regulating anti-neovascular activity. Thus, integrins serve as transmembrane linkers between the ECM and cytoskeleton for outside-in signalling. One such endogenous circulating molecule, tumstatin, a 28-kDa protein from the C-terminal non-collagenous (NC1) domain of alpha3 type IV collagen was identified as an inhibitor of angiogenesis. Tumstatin interacting with alphaVbeta3 integrin and inhibits activation of focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI-3K), serine/threonine kinase (Akt/protein kinase B), mammalian target of rapamycin (mTOR) and prevents dissociation of eukaryotic translation initiation factor 4E (eIF4E) from 4E binding protein (4E-BP1) leading to the inhibition of Cap-dependent translation in proliferating endothelial cells. Recently, we also discovered that tumstatin inhibits hypoxia induced important pro-inflammatory molecule cyclo-oxygenase-2 (COX-2) expression via FAK/Akt/NFkB pathway, leading to decreased tumor angiogenesis in an alpha3beta1 integrin dependent manner (Blood 2007, 110; 1168-1177). We study to understand three such endogenous neovascular inhibitors derived from type IV collagen that include tumstatin, arresten and malignostatin which are involved in cell signalling and the way these proteins control adhesion and migration of endothelial cells in pathological processes involved abnormal vasculogenesis such as diabetic retinopathy and age related macular degeneration.

VITAMIN D STATUS IS ASSOCIATED WITH CARDIOMETABOLIC PARAMETERS AMONG NON-OBESE ARAB CHILDREN AND ADOLESCENTS

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Aim: To determine whether cardiometabolic parameters are influenced by 25-hydroxyvitamin D levels among non-obese Arab youth. **Methods:** This is a multi-center, cross-sectional study done at the Diabetes and Endocrinology Research Lab, King Saud University, Riyadh, KSA. A total of 186 randomly selected Saudi boys (mean age 12.4 ± 3.7 years) and 114 girls (11.6 ± 3.7) with parental consent and participants' assent participated. Anthropometric measurements included body mass index, waist and circumference as well as blood pressure. Fasting blood samples were also collected and serum glucose as well as lipid profile were measured using routine methods. Serum 25-hydroxyvitamin D was quantified using enzyme-linked immunosorbent assay. **Results:** Only 8.9 % of boys and 17.8 % of girls had normal 25-hydroxyvitamin D levels. Severe hypovitaminosis D (< 12.5nmol/l) was noted in 10 % of boys and 9.8 % of girls. Boys had higher cases of severe-moderate hypovitaminosis D as opposed to girls (p =0.038). 25-hydroxyvitamin was inversely correlated to age, BMI, systolic and diastolic blood pressure, waist, hips and triglycerides (and was positively associated to HDL-cholesterol. Age and systolic blood pressure were the significant predictors for 25-hydroxyvitamin D, explaining 31 % of the variance perceived (p = 0.0005). **Conclusion:** Significant inverse associations of serum 25-hydroxyvitamin D to cardiometabolic parameters present promising cardioprotective benefits of vitamin D status correction at an early age either by supplementation or lifestyle modification. Follow up clinical intervention studies are needed to validate hypothesis.

ENVIRONMENTAL EXPOSURE AND BIOMARKERS OF OBESITY

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There has been a substantial increase in the prevalence of obesity at an alarming rate, which indirectly provides increased demand for health care needs, and public health awareness in the Kingdom of Saudi Arabia. The current epidemic in obesity cannot be explained solely by alterations in food intake and/or decrease in exercise. The level of chemicals in the environment is purported to coincide with the incidence of obesity. The ester bond linking bisphenol A (BPA) molecules in polycarbonate and resins undergoes hydrolysis, resulting in the release of free BPA into food, beverages, and the environment. Numerous monitoring studies now show almost ubiquitous human exposure to biologically active levels of this chemical. A recent study suggested that serum concentrations of some of the chemical have been found to be associated with the onset and incidence rate of diabetes mellitus being a risk factor of obesity. Furthermore, it is likely that early BPA exposure can influence several mechanisms important for body weight regulation, including adipocyte deposition, glucose uptake and homeostasis, and the development and maturation of pathways and circuits important for energy homeostasis. In the present review we intended to evaluate biomarkers of the obesity epidemic and the doses associated with the controversial chemical BPA.

EFFECTS OF ROSUVASTATIN ON THE PROGRESSION OF DIABETIC NEPHROPATHY IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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The effects of two different doses of rosuvastatin (ROSV, 1 and 5 mg/kg/day, p.o) on the progression of diabetic nephropathy in streptozotocin (STZ)-induced diabetic rats for eight weeks were investigated. Non diabetic and diabetic adult male Wistar rats were used. Diabetes was induced by a single intraperitoneal injection (i.p.) of STZ (55 mg/ kg). Three days after diabetes induction, rosuvastatin was administered orally once daily, for eight weeks to non diabetic and diabetic rats. Body weight, kidney/body weight (K/BW) ratio, blood glucose level, lipid profile and kidney function indicators including urine volume, urinary total protein, urinary albumin excretion rate (UAER), serum creatinine, and glomerular filtration rate (GFR) were measured. Serum levels of nitrite/nitrate, inflammatory cytokine, intercellular adhesion molecule-1 (ICAM-1) and prosclerotic cytokine, transforming growth factor (TGF-β_1) as well as the oxidative stress marker, 8-hydroxy-2'-deoxy guanosine (8-OHdG) in urine were assessed. Kidney histopathological examination and advanced glycosylation end products (AGE) immunostaining were performed. Treatment of diabetic rats with rosuvastatin corrected lipid profile abnormalities and significantly reduced diabetes-induced increase in serum creatinine level, UAER, serum levels of total nitrite/nitrate, ICAM-1, TGF-β_1 and urinary 8-OHdG. Moreover, histopathological changes and AGE immunostaining-induced by diabetes were suppressed by rosuvastatin. On other hand, rosuvastatin did not affect the elevation of plasma glucose level and body weight loss. These results suggest that rosuvastatin exerts lipid lowering action and important pleiotropic effects through inhibition of oxidative stress and AGE accumulation. The pleiotropic actions of rosuvastatin may offer potential benefits in addition to those associated with lipid lowering in the treatment of diabetic nephropathy.

PREVALENCE OF THYROID ANTIBODIES IN IMPAIRED GLUCOSE TOLERANT AND TYPE2 DIABETIC PAKISTANI SUBJECTS WITH NORMAL THYROID FUNCTION

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Diabetes mellitus and thyroid diseases are the two common endocrine disorders seen in the adult Pakistani population. The association between thyroid autoimmunity and T1DM is well documented. Thyroid antibody testing is not routinely available in Pakistan. Little is known of the risk of autoimmune disease with T2DM. In this study a total of 508 clinically normal euthyroid glycemic anomalies were recruited from an outpatient diabetic clinic. Two main groups of hyperglycemic subjects were targeted, which included IGT and newly diagnosed T2DM groups of either sex. After the initial screening and a preliminary study of glycemic anomalies, which included anthropometric characters, FPG and HbA1c %, these subjects were analyzed for thyroid hormones, TSH, insulin and antibodies to thyroglobulin (TgAb).They were measured by ELISA technique. In this study significantly high titer of thyroglobulin antibodies (p<0.05) among the impaired glucose tolerant and type2 diabetic subjects were observed. The increase in TgAb was more profound in IGT group as compared to the diabetic group. A highly significant positive correlation of TgAb with T_3/T_4 ratio was found in the IGT (r = 0.652, r = 0.871, P<0.01) and diabetic groups, respectively.IR did not show any relationship with TgAb in IGT and diabetic groups (r = 0.084, r = 0.196, respectively). Low incidence of thyroid autoimmunity in T2DM was observed .No comparable data from Pakistan was available to reveal this information. The clinical utility of these antibody measurements requires further evaluation in the glycemic anomalies in pre diabetic state.

STUDY OF URINARY CRYSTALS FOR TYPE I DIABETICS

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Diabetes mellitus is a common public health problem, due to the seriousness of its complications. It could be harmful for the kidneys of these patients and to take preventive therapeutic measures against the various lithiasis. The survey includes 116 diabetics of type I, the first morning urine sample have been examined with a polarized light microscope for qualitative and quantitative analysis of crystalluria. The calcium oxalates were mainly in abundance in both genders compared to the other crystalline species, with a frequency of 79.5% at direct examination and 84.6% at +4°C. The total frequency of purins was 22.0% at direct examination. The crystalluria observed in type I diabetics showed the prevalence of the oxalo-calcic type (Weddelitte) crystals with a frequency of 64.5% followed by Whewellite with 15.0%. The high percentage of the purin crystalluria for diabetics in general, gives an information on dangers to clinicians and experts.

ON THE LOOKOUT FOR THE MOST RELIABLE BIOCHEMICAL AND GENETIC MARKERS FOR CORONARY HEART DISEASE IN SAUDI PATIENTS

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This study aimed to investigate biochemical and genetic markers of CHD in Saudis. The group included 111 individuals suffering from CHD and 369 healthy adult controls. Fasting blood samples, were analysed for biochemical, immunological and hormonal parameters [renal, bone, liver function tests, electrolytes, lipids and lipoproteins, apolipoproteins, immunoglobulins and complement levels, insulin, C-peptide, coagulation parameters, leptin and Lp(a)]. DNA was extracted and used for the analysis of angiotensin converting enzyme (ACE), glycogen synthetase, glucokinase, and paraoxinase (PON) gene polymorphisms. ACE genotypes DD, ID and II showed extensive polymorphism. The frequency of II genotype was higher (11.7 % vs 2.13%), while the DD genotype occurred at a lower prevalence (48.3 % vs 56.03%), in CHD patients. The frequency of S_A genotype A1A1 was significantly higher in the CHD patients (56.06 % vs 40.0%), while that of A1A2 was significantly lower (42.42% vs 59.2%). Paraoxonase (PON) and glycogen synthase genotypes did not show any significant difference in CHD and normal controls. CHD patients showed elevations of Lp(a), leptin, urea, creatinine, alanine amino transferase (ALT), creatinine phospho kinase (CPK), lactate dehydrogenase (LDH), cholesterol, triglyceride, low density lipoprotein (LDL) and LDL-cholesterol, apolipoprotein (apo) B, fibrinogen and apartial thromboplastin time, while apo A1, high density lipoprotein (HDL) and HDL-cholesterol were significantly lower (p<0.05). Majority of patients had significantly elevated leptin and Lp(a) levels. These results in Saudi CHD patients identify the most reliable marker.

BIOMARKER DISCOVERY BASED ON APTAMERS

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Biomarker discovery is one of the newly emerging innovations in the diagnosis and treatment of cancer and many other diseases. Many research groups and large pharmaceutical companies are actively engaged in searching for novel biomarkers for malignant diseases, which will make molecular analysis and monitoring of disease possible. Aptamers are ssDNA, RNA, or modified nucleic acids. They have the ability to bind specifically to their targets, which range from small organic molecules to proteins. Carcinoembryonic antigen (CEA) is a glycoprotein involved in cell adhesion. It is normally produced during fetal development, but the production of CEA stops before birth. So far, no anti-CEA aptamers have been reported. We assessed the hypothesis that whether the aptamer bind to CEA by different assays. The aim of this project was to isolate aptamers against CEA by flow cytometry and microscopy. Briefly, cancer cells were incubated on a multi-well slide overnight. Cells were incubated for two hours at 4°C with deferent aptamers. The slide was then imaged immediately using fluorescence microscopy. Also aptamers and cells were imaged by flow cytometry. Our results showed that these aptamers bind to CEA on the surface of cancerous cell line using flow cytometry and microscopy. We also demonstrated that CEA does not bind to the surface of a CEA negative cell line. In conclusion, the developed anti-CEA aptamers may be useful to use these reagents as *in vitro* diagnostic tools. In such products, aptamers can play a key role either in conjunction with, or in place of, antibodies.

BIOMARKERS IN DRUG DISCOVERY AND DEVELOPMENT

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Biomarkers are objective, measurable biochemical, genetic, or other biological indicators of a physiological or disease process. Biomarkers will facilitate the combination of therapeutics with diagnostics and will thus play an important role in the development of personalized medicine. Biomarkers have always been important in clinical development and provide the most practical means of demonstrating that a candidate drug is safe and effective in a disease target population. There is little doubt that biomarkers will be one of the major drivers of pharmaceutical research and development in the 21st Century. Currently the most important applications of biomarkers are in drug discovery and development. The role of biomarkers in various therapeutic areas particularly cancer, cardiovascular diseases and disorders of the central nervous system, is described. One goal of biomarker development is to enable risk reduction for drug safety and efficacy, thereby reducing attrition of drug during the clinical phases of development. Biomarkers in disease play a vital important role and have gained more importance in drug discovery because most drugs are only effective in 40 to 60% of the patient population. The techniques used in discovery of biomarkers are: Genomics, Proteomics, Transcriptomics, Metabolomics and Biostatistics. By now, a large number of biomarkers have been applied for use in diabetes, obesity, oncology (breast cancer, prostate cancer, colorectal cancer, lung cancer and ovarian cancer), cardiovascular disease, CNS disorders, and infectious diseases. In this article, the application of biomarkers in drug discovery and development has been discussed in details.

T CELL RECEPTOR REARRANGEMENT EXCISION CIRCLES (TREC) AS POTENTIAL BIOMARKERS OF ISCHEMIC HEART DISEASE

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T cell receptor excision circle (TREC) PCR-assay seemed to enable direct detection of recent thymic emigrants in peripheral blood and therefore the quantification of thymic output. We studied TREC level in 3 groups of healthy donors: 16 people. 16 - 30 years old (group 1, TREC Median 0,156299 Units), 8 persons 30 - 45 years old (group 2, TREC Median 0,08782 Units) and 9 people over 45 years (group 3 TREC Median 0,051858 Units). We confirmed age-related decline of thymic output in healthy donors. TREC level in patients with chronic forms of coronary heart disease (age 55 – 70 years old) was lower but comparable with group 3 (TREC Median 0,0200 Units), Unexpectedly high level of TREC comparable with donors group 2 we detected in patients with Acute Myocardial Infarction (AMI) (10 patients, age range 48 – 71 y) (TREC Median 0,089845 Units). Interpretation of these results must take into account the content of TREC in peripheral blood lymphocytes is dependent not only on thymic output, but also on the "peripheral" factors, in particular on survival time of "naive" T cells in periphery. Evidence that the up-regulation of Th1 cell-functions and interferon-γ hyperproduction existed in patients with AMI (but not in patients with unstable or stable angina) 1 week and 1 month after the onset of symptoms. Up-regulation of Th1 cell-functions may participate in the immune-mediated ventricular remodeling and heart failure progression after AMI. The slowing of "naive"-T-cells turnover and Th1/Th2 imbalance could be the reason of TREC increase in AMI patients. In this way TREC level detection could play role of prognostic factor either immune system dysfunction or disease course monitoring factor in AIM. The work is done in framework of project 080401508 sponsored by Russian Foundation of Basic Research. Project director Dr. Goloviznin M.V.

CORONARY HEART DISEASES RISK FACTORS IN OBESE YOUTH

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This study was to examine coronary heart diseases risk factors in non athlete students. 100 non-athlete men (age 23/56± 3/3 yr, height 172/6± 7/45 cm, Body Weight 74/43± 36/81kg) with overweight (BMI >25 kg·m^{-2}), participated. Subjects' informed health and consent questionnaires. Measured variables in this research study were conducted in, first, determine body mass index (BMI), Percentage of Body Fat (PBF) was calculated form multi-component predication equation using skin-fold thicknesses. Skin-fold thicknesses were measured with a Lafayette Caliper (Model 01127) at three sites (Chest, abdominal and thigh). Waist hip ratio index (WHR) measurement with abdominal and hip circumference. In the second stage, first, systolic blood pressure (SBP) and diastolic blood pressure (DBP) with standard clinical methods were measured. Second was determination of serum lipid profiles, blood samples were obtained in fasting state. The results showed a relationship between body composition and some of coronary heart diseases risk factors. Youth stage close to adults and its role in transition of physiological characteristics to next age periods. However significant relationship between PBF with serum lipids and BW with SBP, DBP can be interpreted such that the reduction of body fat and weight control is impact CHD risk factors. Accumulation of fat in fat cells of younger age begins; having proper food habits is the proper way to reduce obesity and CHD risk factors. Since the epidemiological studies indicated TC has biggest role in heart disease, with considering the study results, body composition desirable will be effective to reduce CHD.

LEPTIN, OBESITY AND EXERCISE

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Obesity is a complex disorder characterized by the accumulation of excess adipose tissue that can caused by genetic and environment factors Increase of energy intake and reduce of energy uptake and /or the combined of both of them can be led to obesity. Energy intake and uptake, is impressed by endocrine and nervous systems. Leptin is a hormone which plays a major role in regulation the intake of energy also has great effect on appetite and eating. Leptin, a protein with a helical structure similar to cytokines and a relative mass of 16KDa, assists in the regulation of body weight and energy homestasis. In recent years the potential participation of leptin has been reported to increase arterial pressure and heart rate by peripherally or centrally medicated mechanisms. The finding that leptin is linked to heart disease risk, strongly suggests that fat may be important in heart disease risk. There are several reasons why leptin response and adaptions to exercise may have important ramifications: exercise is known to effectively reduce obesity(fat mass),thus , if leptin level are affected, this may provide some explanation of how exercise affect obesity. Diet and exercise also have documented to reduce leptin levels regardless of weight loss. Exercise training induced reduction in energy balance, improvements in insulin sensitivity alterations in lipid metabolism and unknown factors. This paper is to explain leptin function and the impact that exercise has on blood leptin concentrations.

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